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(71) Applicant *(for all designated States except US)*: LJL BIOSYSTEMS, INC. [US/US]; 404 Tasman Drive, Sunnyvale, CA 94089 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BURTON, William, G. [US/US]; 4709 Arlene Place, Pleasanton, CA 94566 (US). CRAWFORD, Kimberly, L. [US/US]; 643 Vista Drive, Redwood City, CA 94062 (US). DESHPANDE, Sudhir, S. [IN/US]; 250 Santa Fe Terrace #107, Sunnyvale, CA 94086 (US). EDWARDS, Glenn, R. [US/US]; 231 Chestnut Avenue, Palo Alto, CA 94306 (US). EL-HAGE, Amer [US/US]; 2101 Manzanita Avenue, Menlo Park, CA 94025 (US). FRENCH, Todd, E. [US/US]; 19975 Brenda Court, Cupertino, CA 95014 (US). LEMBERG, Vladimir [IL/US]; 700 Baltic Circle, Redwood City, CA 94065 (US). LEYTES, Joseph, S. [US/US]; 660 Mariposa Avenue #3, Mountain View, CA 94041 (US). MARQUISS, Samuel, A. [US/US]; 2388 Stanford Place, Santa Clara, CA 95051 (US). MEADOWS, John, W. [GB/US]; 28025 Arostadero Road, Los Altos Hills, CA 94022 (US). MINEYEV, Irina [US/US]; 1428 Portola Drive, San Francisco, CA 94127 (US). MODLIN, Douglas, N. [US/US]; 4063 Scripps Avenue, Palo Alto, CA 94036 (US). OWICKI, John, C. [US/US]; 956 North California Avenue, Palo Alto, CA 94303 (US). PETERSON, Jon, F. [US/US]; 1006 Vera Avenue, Redwood City, CA 94061 (US). RICHARDSON, Derrick, A. [US/US]; 2245 Latham Street #8, Mountain View, CA 94040 (US). STELLMACHER, Rick, V. [US/US]; 3155 Drywood Lane, San Jose, CA 95132 (US). TAYLOR, Michael, T. [US/US]; 6304 Buena Vista Drive #C, Newark, CA 94560 (US).

(74) Agents: ABNEY, James, R. et al.; Kolisch, Hartwell, Dickinson, McCormack & Heuser, Suite 200, 520 S.W. Yamhill Street, Portland, OR 97204 (US).

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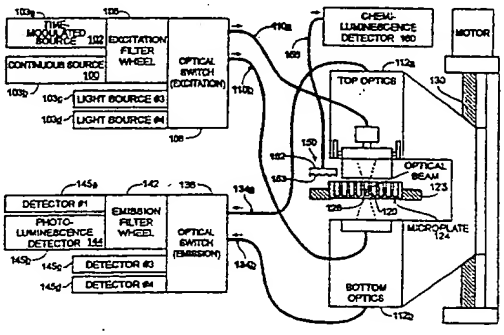

(57) Abstract

A high-throughput light detection instrument and method are described. In some embodiments, switch mechanisms (108, 136) and optical relay structures permit different light sources (103a-d) and/or detectors (145a-d) to be selected for different applications. In other embodiments, switch mechanisms (108, 136) and optical paths permit top/bottom illumination and/or top/bottom detection, or combinations thereof.

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LIGHT DETECTION DEVICE

Cross-References to Related Applications

This application is a continuation of the following U.S. Patent Application, which is incorporated herein by reference: Serial No. 09/062,472, filed April 17, 1998. This application is based upon and claims benefit under 35 U.S.C. § 119 of the following U.S. Provisional Patent Applications, each of which is incorporated herein by reference: Serial No. 60/052,876, filed July 16, 1997; Serial No. 60/059,639, filed September 20, 1997; Serial No. 60/063,811, filed October 31, 1997; Serial No. 60/072,499, filed January 26, 1998; Serial No. 60/072,780, filed January 27, 1998; Serial No. 60/075,414, filed February 20, 1998; Serial No. 60/075,806, filed February 24, 1998; Serial No. 60/082,253, filed April 17, 1998; Serial No. 60/084,167, filed May 4, 1998; Serial No. 60/085,335, filed May 13, 1998; Serial No. 60/085,500, filed May 14, 1998; and Serial No. 60/089,848, filed June 19, 1998.

Field of the Invention

The invention relates to instrumentation and methods for detecting light. More particularly, the invention relates to instrumentation and methods for detecting light using a versatile, sensitive, high-throughput screening apparatus.

Background of the Invention

High-throughput screening instruments are critical tools in the pharmaceutical research industry and in the process of discovering and developing new drugs. The drug discovery process involves synthesis and testing, or screening, of candidate drug compounds against a target. A candidate drug compound is a molecule that might mediate a disease by its effect on a target. A target is a biological molecule, such as an enzyme, receptor, other protein, or nucleic acid, that is believed to play a role in the onset or progression of a disease or a symptom of a disease. Figure 1 shows stages of the drug discovery process, which include target identification, compound

synthesis, assay development, screening, secondary screening of hits, and lead compound screening, or optimization, and finally clinical evaluation.

Targets are identified based on their anticipated role in the progression or prevention of a disease. Until recently, scientists using conventional methods had identified only a few hundred targets, many of which have not been comprehensively screened. Recent developments in molecular biology and genomics have led to a dramatic increase in the number of targets available for drug discovery research.

After a target is selected, a library of compounds is selected to screen against the target. Compounds historically have been obtained from natural sources or synthesized one at a time. Compound libraries were compiled over decades by pharmaceutical companies using conventional synthesis techniques. Recent advances in combinatorial chemistry and other chemical synthesis techniques, as well as licensing arrangements, have enabled industrial and academic groups greatly to increase the supply and diversity of compounds available for screening against targets. As a result, many researchers are gaining access to libraries of hundreds of thousands of compounds in months rather than years.

Following selection of a target and compound library, the compounds must be screened to determine their effect on the target, if any. A compound that has an effect on the target is defined as a hit. A greater number of compounds screened against a given target results in a higher statistical probability that a hit will be identified.

Prior to screening compounds against a target, a biological test or assay must be developed. An assay is a combination of reagents that is used to measure the effect of a compound on the activity of a target. Assay development involves selection and optimization of an assay that will measure performance of a compound against the selected target. Assays are broadly classified as either biochemical or cellular. Biochemical assays usually are performed with purified molecular targets, which generally have certain

advantages, such as speed, convenience, simplicity, and specificity. Cellular assays are performed with living cells, which may sacrifice speed and simplicity, but which may provide more biologically relevant information. Researchers use both biochemical and cellular assays in drug discovery research.

Biochemical and cellular assays may use a variety of detection modalities, including photoluminescence, chemiluminescence, and absorbance. Photoluminescence and chemiluminescence assays involve determining the amount of light that is emitted from excited electronic states created by absorption of light and certain chemical reactions, respectively. Absorbance assays involve determining the amount of light that is transmitted through a composition relative to the amount of light incident on the composition.

Each detection modality may use a variety of equipment. For example, photoluminescence assays typically employ at least a light source, detector, and filter; absorbance assays typically employ at least a light source and detector; and chemiluminescence assays typically employ at least a detector. Moreover, the type of light source, detector, and/or filter employed typically varies even within a single detection modality. For example, among photoluminescence assays, photoluminescence intensity and steady-state photoluminescence polarization assays may use a continuous light source, and time-resolved photoluminescence polarization assays may use a time-varying light source.

Adding to this variability, the types of assays that are desired for high-throughput screening are evolving constantly. As new assays are developed in research laboratories, tested, and published in literature or presented at scientific conferences, new assays become popular and many become available commercially. New analytical equipment may be required to support the most popular commercially available assays.

After selection of a target, compound library, and assay, assays are run to identify promising compound candidates or hits. Once a compound is

identified as a hit, a number of secondary screens are performed to evaluate its potency and specificity for the intended target. This cycle of repeated screening continues until a small number of lead compounds are selected. The lead compounds are optimized by further screening. Optimized lead compounds with the greatest therapeutic potential may be selected for clinical evaluation.

Due to the recent dramatic increase in the number of available compounds and targets, a bottleneck has resulted at the screening stage of the drug discovery process. Historically, screening has been a manual, time-consuming process. Recently, screening has become more automated, and standard high-density containers known as microplates have been developed to facilitate automated screening. Microplates are substantially rectilinear containers that include a plurality of sample wells for containing a plurality of samples. Ninety-six-well microplate formats have been and still are commonly used throughout the high-throughput screening industry. However, some high-throughput screening laboratories are using 384- and 768-well plates, and some laboratories are experimenting with 1536-, 3456-, and 9600-well microplates.

Figure 2 shows a stack of overlapping microplates with various well densities. Plate 30 has 96 wells. Plate 32 has 384 wells. Plate 34 has 1536 wells. Plate 36 has 3456 wells. Plate 38 has 9600 wells. Figure 2 illustrates the substantial differences in well dimensions and densities that may be used in high-throughput screening assays. Many analyzers are not flexible enough to read microplates having different numbers of wells, such that it currently may be necessary to provide different analyzers for different modes of analysis. Moreover, many analyzers are not sensitive or accurate enough to read results from the smaller wells associated with the higher-density microplates. Inadequate sensitivity may result in missed hits, limited research capabilities, increased costs of compounds, assays, and reagents, and lower throughput.

Screening an increasing number of compounds against an increasing number of targets requires a system that can operate with a high degree of automation, analytical flexibility, and speed. In particular, because

high-throughput applications may involve repeating the same operations hundreds of thousands of times, even the smallest shortcomings are greatly magnified. Current screening systems operate with various degrees of automation. Automation, from sample dispensing to data collection, enables round-the-clock operation, thereby increasing the screening rate. Automated high-throughput screening systems usually include combinations of assay analyzers, liquid handling systems, robotics, computers for data management, reagents and assay kits, and microplates.

Most analyzers in use today are not designed specifically for high-throughput screening purposes. They are difficult and expensive to integrate into a high-throughput screening environment. Even after the analyzer is integrated into the high-throughput screening environment, there often are many problems, including increased probability of system failures, loss of data, time delays, and loss of costly compounds and reagents.

In addition, most analyzers in use today offer only a single assay modality, such as absorbance or chemiluminescence, or a limited set of modalities with non-optimum performance. To perform assays using different detection modes, researchers generally must switch single-mode analyzers and reconfigure the high-throughput screening line. Alternatively, researchers may set up the high-throughput screening line with multiple single-mode analyzers, which often results in critical space constraints.

Thus, prior detection devices generally have not recognized the need to provide analytic flexibility and high performance for assay development as well as ease of use and smooth automation interface for the high-throughput screening laboratory. A real need exists for a versatile, sensitive, high-throughput screening apparatus and components thereof that can handle multiple detection modalities and wide ranges of sample volumes and variations in container material, geometry, size, and density format while reliably maintaining a high level of sensitivity.

Summary of the Invention

The present invention addresses these and other shortcomings by providing instrumentation and methods for detecting light transmitted from a composition.

In some embodiments, the instrumentation and methods emphasize a light detection device. The light detection device may have plural light sources and/or detectors, or top/bottom illumination and/or detection. The light detection device also may have the capability of transmitting light substantially exclusively from a sensed volume of the composition The light detection device also may combine photoluminescence detection with chemiluminescence detection.

In other embodiments, the instrumentation and methods emphasize components of a light detection device. The components may include a floating head assembly for transmitting light through an aperture in a surface substantially without leakage. The components also may include filter cartridges for holding optical filters, and optical filter holder assemblies for holding such filter cartridges. The components also may include moveable control units that may be mounted at any one of a plurality of docking locations. The components also may include mechanisms for supporting a microplate, and for feeding a microplate in and out of an analyzer.

The nature of the invention will be understood more readily after consideration of the drawings and the detailed description of the preferred embodiments that follow.

Brief Description of the Figures

Figure 1 is a flow chart showing elements of the drug discovery process.

Figure 2 is a top view of overlapping microplates showing variations in well density.

Figure 3 is a schematic view of analyzer components employed in an embodiment of the invention.

Figure 4 is a schematic partial perspective view of analyzer components employed in an embodiment of the invention.

Figure 5 is a schematic view of optical components of a luminescence optical system employed in an embodiment of the invention.

Figure 6 is a schematic view of optical components of a chemiluminescence optical system employed in an embodiment of the invention.

Figure 7 is a cross-sectional perspective view of a top optics head employed in an embodiment of the invention.

Figure 8 is a cross-sectional perspective view of an alternative top optics head employed in an embodiment of the invention.

Figure 9 is a partially schematic cross-sectional view of a chemiluminescence head employed in an embodiment of the invention.

Figure 10 is a cross-sectional perspective view of a portion of the chemiluminescence head shown in Figure 8.

Figure 11 is a partial perspective view of top and bottom optics heads employed in an embodiment of the invention.

Figure 12 is a partially schematic side elevation view of the optics assembly shown in Figure 11, showing an offset between the top and bottom optics head and side illumination.

Figures 13-16 are schematic views of sensed volumes in microplate wells.

Figure 17 is a schematic top view of a microplate.

Figure 18 is a graph showing the relationships between critical Z-height and microplate well height.

Figure 19 is a partial perspective, partial schematic view of a light source module employed in an embodiment of the invention.

Figure 20 is a partial perspective view of an alternative light source module.

Figure 21 is a partial perspective, partial schematic view of a detector module employed in an embodiment of the invention.

Figure 22 is a partial perspective view of an alternative light source module.

Figure 23 is a partial perspective view of a fiber optic shuttle assembly employed in an embodiment of the invention.

Figure 24 is a perspective view of a floating head assembly employed in the fiber optic shuttle assembly shown in Figure 23.

Figure 25 is a cross-sectional view of the floating head assembly, taken generally along the line 25-25 in Figure 24.

Figure 26 is a perspective view of an alternative floating head assembly.

Figure 27 is a cross-sectional view of the alternative floating head assembly, taken generally along the line 27-27 in Figure 26.

Figure 28 is a partially exploded perspective view of an optical filter wheel assembly employed in an embodiment of the invention.

Figure 29 is a partially exploded perspective view of a portion of an optical filter wheel assembly like that shown in Figure 1, showing a mechanism by which short filter cartridges may be removed.

Figure 30 is a partially exploded perspective view of the portion of the optical filter wheel assembly shown in Figure 29, showing a mechanism by which tall filter cartridges may be removed.

Figure 31 is a perspective view showing a mechanism by which optical filters may be placed in a tall filter cartridge.

Figure 32 is a perspective view showing a mechanism by which a friction member may be pressed into place using a funnel and slug.

Figure 33 is a top view of a short filter cartridge employed in an embodiment of the invention.

Figure 34 is a cross-sectional view of the short filter cartridge, taken generally along the line 34-34 in Figure 33.

Figure 35 is a top view of a short filter cartridge employed in an embodiment of the invention.

Figure 36 is a cross-sectional view of the short filter cartridge, taken generally along the line 36-36 in Figure 35.

Figure 37 is a top view of a funnel structure employed in conjunction with an embodiment of the invention.

Figure 38 is a cross-sectional view of the funnel structure, taken generally along the line 38-38 in Figure 37.

Figure 39 is a perspective view of a pivotable filter cartridge employed in an embodiment of the invention.

Figure 40 is a perspective view of the top of a transporter assembly employed in an embodiment of the invention.

Figure 41 is a perspective view of the bottom of the transporter assembly shown in Figure 40.

Figure 42 is a partial cross-sectional view of the transporter assembly, taken generally along the line 42-42 in Figure 41.

Figure 43 is a perspective view of a base and associated drive mechanisms for moving a transporter along X and Y axes relative to the base.

Figure 44 is a partially exploded perspective view of a housing for an analyzer of the present invention.

Figure 45 is a front view of the control unit shown in Figure 44.

Figure 46 is a top view of one of the control interface docking locations shown in Figure 44.

Figure 47 is a front view of the input/output panel shown in Figure 44.

Figure 48 is a perspective view of sample feeder 890 with bins removed so that the internal mechanisms of the feeder can be viewed.

Figures 49A and 49B are cross-sections through the first station of sample feeder 890 showing latch and lifter cooperation to remove a microplate from the bottom of a stack.

Figures 50A and 50B are cross-sectional views through the output station of sample feeder 890 showing latch and lifter cooperation to add a microplate to the bottom of a stack.

Detailed Description of the Invention

The invention provides an analyzer capable of supporting a wide range of assay formats that can be carefully selected and fine-tuned for screening desired targets with flexibility, durability, and convenience. Flexibility means that the analyzer can be used with a variety of samples and sample assays. Durability means that the analyzer can be used repeatedly, at high throughput, in laboratory and industrial settings. Convenience means that the analyzer can be used with only minimal user intervention., while also allowing assays to be run in smaller containers with reduced volumes.

The analyzer achieves these and other objectives, in part, by employing an optical system that minimizes sample interfacial boundary interference, thereby permitting reduction in assay volume in existing formats such as 96 or 384 well plates, and utilization of denser formats such as 768, 1536, 3456, or 9600 well plates. The analyzer also achieves these objective, in part, by providing the ability automatically to switch between different modes, including absorbance, photoluminescence, photoluminescence polarization, time-resolved photoluminescence, photoluminescence lifetime, and chemiluminescence modalities, among others.

The apparatus of the present invention generally includes a stage for supporting a composition in an examination site, an automated registration device for bringing successive compositions and the examination site into register for analysis of the compositions, a light source for delivering light into the compositions, a detector for receiving light transmitted from the compositions, and an optical relay structure for transmitting light substantially exclusively from a sensed volume that may comprise only a portion of the composition.

Description of the Optical System

Figures 3-6 show a preferred embodiment of the optical system of an analyzer 50 constructed in accordance with the present invention. The optical system generally includes at least one light source for delivering light to a composition, at least one detector for receiving light transmitted from the composition, and an optical relay structure for relaying light between the light source, composition, and detector. The optical system may limit detection to a sensed volume that may comprise only a portion of the composition.

Components of the optical system are chosen to optimize sensitivity and dynamic range for each assay mode supported by the analyzer. Toward this end, optical components with low intrinsic luminescence are chosen. In addition, some components are shared by different modes, whereas other components are unique to a particular mode. For example, photoluminescence intensity and steady-state photoluminescence polarization modes share a light source; time-resolved luminescence modes use their own light source; and chemiluminescence modes do not use a light source. Similarly, photoluminescence and chemiluminescence modes use different detectors.

These assay modes all involve detection of luminescence, which is the emission of light from excited electronic states of atoms or molecules. Luminescence generally refers to all kinds of light emission, except incandescence, and may include photoluminescence, chemiluminescence, and electrochemiluminescence, among others. In photoluminescence, including fluorescence and phosphorescence, the excited electronic state is created by the absorption of electromagnetic radiation. In chemiluminescence, which includes bioluminescence, the excited electronic state is created by a transfer of chemical energy. In electrochemiluminescence, the excited electronic state is created by an electrochemical process.

Separate descriptions of the photoluminescence and chemiluminescence optical systems are presented below. Selected components

of both systems are described in greater detail in subsequent sections. The optical system presented here is a preferred embodiment. The present invention also includes other arrangements and components capable of detecting light from a sensed volume in high-throughput applications.

Photoluminescence optical system. Figures 3-5 show the photoluminescence optical system of analyzer 50. Because photoluminescence follows the absorption of light, the photoluminescence optical system must include one or more light sources. In analyzer 50, there are two light sources. A continuous source 100 provides light for photoluminescence intensity and steady-state photoluminescence polarization assays. A preferred continuous source is a high-intensity, high-color temperature xenon arc lamp. The preferred source provides more light per unit time than flash sources, increasing sensitivity and reducing read times. A time-modulated source 102 provides light for time-resolved photoluminescence assays, such as photoluminescence lifetime and time-resolved photoluminescence polarization assays. A preferred time-modulated source is a xenon flash lamp. The preferred source produces a "flash" of light for a brief interval before signal detection and is especially well suited for time-domain measurements. Other time-modulated sources include pulsed lasers, as well as continuous lamps whose intensity can be modulated extrinsically using a Pockels cell, Kerr cell, or other mechanism. The latter sources are especially well suited for frequency-domain measurements. Analyzer 50 includes light source slots 103a-d for four light sources, although other numbers of light source slots and light sources also could be provided. The direction of light transmission through the photoluminescence optical system is indicated by arrows.

More generally, light sources include any sources of electromagnetic radiation of any wavelength capable of inducing photoluminescence or absorption in a composition. For example, light includes but is not limited to ultraviolet, visible, and infrared radiation. Suitable light sources include lamps, electroluminescence devices, lasers, light-emitting

diodes (LEDs), and particle accelerators. Depending on the source and assay mode, light produced by such light sources may be 1) mono- or multichromatic, 2) polarized or unpolarized, 3) coherent or incoherent, and/or 4) continuous or time-modulated.

In analyzer 50, continuous source 100 and time-modulated source 102 produce multichromatic, unpolarized, and incoherent light. Continuous source 100 produces substantially continuous illumination, whereas time-modulated source 102 produces time-modulated illumination. Light from these light sources may be delivered to the sample without modification, or it may be filtered to alter its intensity, spectrum, polarization, or other properties.

Light produced by the light sources follows an excitation optical path to an examination site. Such light may pass through one or more "spectral filters," which generally comprise any mechanism for altering the spectrum of light that is delivered to the sample. Spectrum refers to the wavelength composition of light. A spectral filter may be used to convert white or multichromatic light, which includes light of many colors, into red, blue, green, or other substantially monochromatic light, which includes light of one or only a few colors. In analyzer 50, spectrum is altered by an excitation interference filter 104, which selectively transmits light of preselected wavelengths and selectively absorbs light of other wavelengths. For convenience, excitation interference filters 104 may be housed in an excitation filter wheel 106, which allows the spectrum of excitation light to be changed by rotating a preselected filter into the optical path. Spectral filters also may separate light spatially by wavelength. Examples include gratings, monochromators, and prisms.

Spectral filters are not required for monochromatic ("single color") light sources, such as certain lasers, which output light of only a single wavelength. Therefore, excitation filter wheel 106 may be mounted in the optical path of some light source slots 103a,b, but not other light source slots 103c,d.

Light next passes through an excitation optical shuttle (or switch) 108, which positions an excitation fiber optic cable 110a,b in front of the appropriate light source to deliver light to top or bottom optics heads 112a,b, respectively. The optics heads include various optics for delivering light into the sensed volume and for receiving light transmitted from the sensed volume. Light is transmitted through a fiber optic cable much like water is transmitted through a garden hose. Fiber optic cables can be used easily to turn light around corners and to route light around opaque components of the analyzer. Moreover, fiber optic cables give the light a more uniform intensity profile. A preferred fiber optic cable is a fused silicon bundle, which has low autofluorescence. Despite these advantages, light also can be delivered to the optics heads using other mechanisms, such as mirrors.

Light arriving at the optics head may pass through one or more excitation "polarization filters," which generally comprise any mechanism for altering the polarization of light. Polarization refers to the direction of the electric field associated with light. Excitation polarization filters may be included with the top and/or bottom optics head. In analyzer 50, polarization is altered by excitation polarizers 114, which are included only with top optics head 112a. Excitation polarization filters 114 may include an s-polarizer S that passes only s-polarized light, a p-polarizer P that passes only p-polarized light, and a blank O that passes substantially all light. Excitation polarizers 114 also may include a standard or ferro-electric liquid crystal display (LCD) polarization switching system. Such a system is faster and more economical than a mechanical switcher. Excitation polarizers 114 also may include a continuous mode LCD polarization rotator with synchronous detection to increase the signal-to-noise ratio in polarization assays.

Light at one or both optics heads also may pass through an excitation "confocal optics element," which generally comprises any mechanism for focusing light into a "sensed volume." In analyzer 50, the confocal optics element includes a set of lenses 117a-c and an excitation

aperture 116 placed in an image plane conjugate to the sensed volume, as shown in Figure 5. Lenses 117a,b project an image of this aperture onto the sample, so that only a preselected or sensed volume of the sample is illuminated.

Light traveling through the optics heads is reflected and transmitted through a beamsplitter 118, which delivers reflected light to a composition 120 and transmitted light to a light monitor 122. Reflected and transmitted light both pass through lens 117b, which is operatively positioned between beamsplitter 118 and composition 120. The beamsplitter is changeable, so that it may be optimized for different assay modes or compositions. The light monitor is used to correct for fluctuations in the intensity of light provided by the light sources; such corrections are performed by reporting detected intensities as a ratio over corresponding times of the luminescence intensity measured by the detector to the excitation light intensity measured by the light monitor. The light monitor also can be programmed to alert the user if the light source fails. A preferred light monitor is a silicon photodiode with a quartz window for low autofluorescence.

The composition (or sample) is held in a sample container supported by a stage 123. The composition can include compounds, mixtures, surfaces, solutions, emulsions, suspensions, cell cultures, fermentation cultures, cells, tissues, secretions, and/or derivatives and/or extracts thereof. Analysis of the compositions may involve measuring the presence, concentration, or physical properties of a photoluminescent analyte in such a composition. The sample container can include microplates, gene chips, or any array of samples in a known format. In analyzer 50, the preferred sample container is a microplate 124, which includes a plurality of microplate wells 126 for holding compositions. Composition may refer to the contents of a single microplate well, or several microplate wells, depending on the assay.

The position of the sensed volume within the composition created by the confocal optics element can be moved precisely to optimize the signal-

to-noise and signal-to-background ratios. In analyzer 50, position in the X,Y-plane perpendicular to the optical path is controlled by moving the stage supporting the composition, whereas position along the Z-axis parallel to the optical path is controlled by moving the optics heads using a Z-axis adjustment mechanism 130, as shown in Figures 3 and 4. However, any mechanism for bringing the sensed volume into register or alignment with the appropriate portion of the composition also may be employed.

The combination of top and bottom optics permits assays to combine: (1) top illumination and top detection, or (2) top illumination and bottom detection, or (3) bottom illumination and top detection, or (4) bottom illumination and bottom detection. Same-side illumination and detection (1) and (4) is referred to as "epi" and is preferred for photoluminescence assays. Opposite-side illumination and detection (2) and (3) is referred to as "trans" and is preferred for absorbance assays. In analyzer 50, epi modes are supported, so the excitation and emission light travel the same path in the optics head. However, trans modes also could be supported and would be essential for absorbance assays. Generally, top optics can be used with any sample container having an open top, whereas bottom optics can be used only with sample containers having optically transparent bottoms, such as glass or thin plastic bottoms.

Light is transmitted by the composition in multiple directions. A portion of the transmitted light will follow an emission pathway to a detector. Transmitted light passes through lens 117c and may pass through an emission aperture 131 and/or an emission polarizer 132. In analyzer 50, the emission aperture is placed in an image plane conjugate to the sensed volume and transmits light substantially exclusively from this sensed volume. In analyzer 50, the emission apertures in the top and bottom optical systems are the same size as the associated excitation apertures, although other sizes also may be used. The emission polarizers are included only with top optics head 112a. The

emission aperture and emission polarizer are substantially similar to their excitation counterparts.

Excitation polarizers 114 and emission polarizers 132 may be used together in nonpolarization assays to reject certain background signals. Luminescence from the sample container and from luminescent molecules adhered to the sample container is expected to be polarized, because the rotational mobility of these molecules should be hindered. Such polarized background signals can be eliminated by "crossing" the excitation and emission polarizers, that is, setting the angle between their transmission axes at 90°. To increase signal level, beamsplitter 118 should be optimized for reflection of one polarization and transmission of the other polarization. This method will work best where the luminescent molecules of interest emit relatively unpolarized light, as will be true for small luminescent molecules in solution.

Transmitted light next passes through an emission fiber optic cable 134a,b to an emission optical shuttle (or switch) 136. This shuttle positions the appropriate emission fiber optic cable in front of the appropriate detector. In analyzer 50, these components are substantially similar to their excitation counterparts, although other mechanisms also could be employed.

Light exiting the fiber optic cable next may pass through one or more emission "intensity filters," which generally comprise any mechanism for reducing the intensity of light. Intensity refers to the amount of light per unit area per unit time. In analyzer 50, intensity is altered by emission neutral density filters 138, which absorb light substantially independent of its wavelength, dissipating the absorbed energy as heat. Emission neutral density filters 138 may include a high-density filter H that absorbs most incident light, a medium-density filter M that absorbs somewhat less incident light, and a blank O that absorbs substantially no incident light. These filters are changed by hand, although other methods also could be employed, such as a filter wheel. Intensity filters also may divert a portion of the light away from the sample without absorption. Examples include beam splitters, which transmit

some light along one path and reflect other light along another path, and Pockels cells, which deflect light along different paths through diffraction.

Light next may pass through an emission interference filter 140, which may be housed in an emission filter wheel 142. In analyzer 50, these components are substantially similar to their excitation counterparts, although other mechanisms also could be employed. Emission interference filters block stray excitation light, which may enter the emission path through various mechanisms, including reflection and scattering. If unblocked, such stray excitation light could be detected and misidentified as photoluminescence, decreasing the signal-to-background ratio. Emission interference filters can separate photoluminescence from excitation light because photoluminescence has longer wavelengths than the associated excitation light.

The relative positions of the spectral, intensity, polarization, and other filters presented in this description may be varied without departing from the spirit of the invention. For example, filters used here in only one optical path, such as intensity filters, also may be used in other optical paths. In addition, filters used here in only top or bottom optics, such as polarization filters, may also be used in the other of top or bottom optics or in both top and bottom optics. The optimal positions and combinations of filters for a particular experiment will depend on the assay mode and the composition, among other factors.

Light last passes to a detector, which is used in absorbance and photoluminescence assays. In analyzer 50, there is one photoluminescence detector 144, which detects light from all photoluminescence modes. A preferred detector is a photomultiplier tube (PMT). Analyzer 50 includes detector slots 145a-d for four detectors, although other numbers of detector slots and detectors also could be provided.

More generally, detectors comprise any mechanism capable of converting energy from detected light into signals that may be processed by the analyzer. Suitable detectors include photomultiplier tubes, photodiodes,

avalanche photodiodes, charge-coupled devices (CCDs), and intensified CCDs, among others. Depending on the detector and assay mode, such detectors may be used in (1) photon-counting or continuous modes, and (2) imaging or integrating modes.

Chemiluminescence optical system. Figures 3, 4, and 6 show the chemiluminescence optical system of analyzer 50. Because chemiluminescence follows a chemical event rather than the absorption of light, the chemiluminescence optical system does not require a light source or other excitation optical components. Instead, the chemiluminescence optical system requires only selected emission optical components. In analyzer 50, a separate lensless chemiluminescence optical system is employed, which is optimized for maximum sensitivity in the detection of chemiluminescence.

Generally, components of the chemiluminescence optical system perform the same functions and are subject to the same caveats and alternatives as their counterparts in the photoluminescence optical system. The chemiluminescence optical system also can be used for other assay modes that do not require illumination, such as electrochemiluminescence.

The chemiluminescence optical path begins with a chemiluminescent composition 120 held in a sample container 126. The composition and sample container are analogous to those used in photoluminescence assays; however, analysis of the composition involves measuring the intensity of light generated by a chemiluminescence reaction within the composition rather than by light-induced photoluminescence. A familiar example of chemiluminescence is the glow of the firefly.

Chemiluminescence light typically is transmitted from the composition in all directions, although most will be absorbed or reflected by the walls of the sample container. A portion of the light transmitted through the top of the well is collected using a chemiluminescence head 150, as shown in Figure 3, and will follow a chemiluminescence optical pathway to a detector.

The direction of light transmission through the chemiluminescence optical system is indicated by arrows.

The chemiluminescence head includes a nonconfocal mechanism for transmitting light from a sensed volume within the composition. Detecting from a sensed volume reduces contributions to the chemiluminescence signal resulting from "cross talk," which is pickup from neighboring wells. The nonconfocal mechanism includes a chemiluminescence baffle 152, which includes rugosities 153 that absorb or reflect light from other wells. The nonconfocal mechanism also includes a chemiluminescence aperture 154 that further confines detection to a sensed volume.

Light next passes through a chemiluminescence fiber optic cable 156. This fiber optic cable is analogous to excitation and emission fiber optic cables 110a,b and 134a,b in the photoluminescence optical system. Fiber optic cable 156 may include a transparent, open-ended lumen that may be filled with fluid. This lumen would allow the fiber optic to be used both to transmit luminescence from a microplate well and to dispense fluids into the microplate well. The effect of such a lumen on the optical properties of the fiber optic could be minimized by employing transparent fluids having optical indices matched to the optical index of the fiber optic.

Light next passes through one or more chemiluminescence intensity filters, which generally comprise any mechanism for reducing the intensity of light. In analyzer 50, intensity is altered by chemiluminescence neutral density filters 158. Light also may pass through other filters, if desired.

Light last passes to a detector, which converts light into signals that may be processed by the analyzer. In analyzer 50, there is one chemiluminescence detector 160. This detector may be selected to optimize detection of blue/green light, which is the type most often produced in chemiluminescence. A preferred detection is a photomultiplier tube, selected for high quantum efficiency and low dark count at chemiluminescence wavelengths (400-500 nanometers).

Optics Heads and the Generation of Sensed Volumes

Figure 7 shows a cross-sectional view of top optics head 112a, which is used together with fiber optic cables 110a, 134a and apertures 116, 131, as shown in Figure 5, to create the sensed volume. Top optics head 112a is substantially similar to bottom optics head 112b, as shown in Figures 11 and 12, except that top optics head 112a includes chemiluminescence head 150 and excitation and emission polarizers 114, 132 (not shown), and that bottom optics head 112b includes a window and drip lip (described below).

Excitation light arrives at top optics head 112a through excitation fiber optic cable 110a. Fiber optic cables are cylindrical waveguides that transmit light through a process known as total internal reflection. Fiber optic cables are characterized by a numerical aperture, which describes the maximum angle through which the fiber optic cable can collect light for total internal reflection. The higher the numerical aperture, the greater the angle over which the fiber optic cable can collect and transmit light. The numerical aperture is defined as $NA = n\sin\theta$, where NA is the numerical aperture, n is the index of refraction of the medium adjacent the fiber optic cable, and θ is the half angle of the cone of transmitted or incident light. In top optics head 112a, the medium adjacent the fiber optic cable is air, so $n \cong 1$.

Excitation light exits fiber optic cable 110a through excitation aperture 116 at a cone angle θ_1 determined in part by the numerical aperture of the fiber optic cable. In top optics head 112a, exiting excitation light forms a first cone 170 of excitation light, with its apex positioned just inside the tip 172 of fiber optic cable 110a. First cone 170 of excitation light passes through an excitation polarizer 114 (not shown), and then through a first plano-convex converging lens 174, whose plan side 176 is oriented toward fiber optic cable 110a. First lens 174 is positioned so that it substantially converts first cone 170 of excitation light into a first cylinder 178 of excitation light. This conversion is accomplished by positioning tip 172 substantially at the focal point of first lens 174.

First cylinder 178 of excitation light impinges on beamsplitter 118a. Beamsplitter 118a reflects a reflected cylinder portion 180 of excitation light toward composition 120 in sample well 126. Reflected cylinder portion 180 passes through a second plano-convex converging lens 182, whose plan side 184 is oriented away from beamsplitter 118a. Second lens 182 converts reflected cylinder portion 180 of excitation light into a second cone 186 of excitation light, which is focused onto and thus delivered to composition 120 in sample well 126. The cone angle θ_2 of second cone 186 is determined in part by the numerical aperture of second lens 182, and may be different from the cone angle θ_1 describing excitation light exiting fiber optic cable 110a.

Beamsplitter 118a also transmits a transmitted cylinder portion 188 of the excitation light to light monitor 122, which functions as described above. The optics used to focus the transmitted light into the light monitor may be substantially similar to the optics used to focus the reflected light into the sample well. Alternatively, the optics may include a lensless system, such as a black tapered cone to direct light.

The excitation light may induce photoluminescence within the composition. Photoluminescence (or emission) light has longer wavelengths than the associated excitation light. This is due to conservation of energy; in photoluminescence, the emission light has lower energy (and so longer wavelength) than the excitation light, because some of the energy of the excitation light is lost nonradiatively.

A conical portion of the emission light substantially coextensive with second cone 186 of excitation light passes back through second lens 182, which converts the conical portion into a cylindrical portion of emission light substantially coextensive with reflected cylinder 180 of excitation light.

Emission light next impinges on beamsplitter 118a, which transmits a cylinder portion 190 of emission light toward photoluminescence detector 144. Beamsplitter 118a typically is chosen to accommodate one of two different scenarios. If a large number or variety of luminescent molecules are to

be studied, the beamsplitter must be able to accommodate light of many wavelengths; in this case, a "50:50" beamsplitter that reflects half and transmits half of the incident light independent of wavelength is optimal. Such a beamsplitter can be used with many types of molecules, while still delivering considerable excitation light onto the composition, and while still transmitting considerable emission light to the detector. If one or a few related luminescent molecules are to be studied, the beamsplitter needs only to be able to accommodate light at a limited number of wavelengths; in this case, a "dichroic" or "multichroic" beamsplitter is optimal. Such a beamsplitter can be designed for the appropriate set of molecules and will reflect most or substantially all of the excitation light, while transmitting most or substantially all of the emission light. This is possible because the reflectivity and transmissivity of the beamsplitter can be varied with wavelength.

Cylinder portion 190 of emission light transmitted through beamsplitter 118a passes through a third plano-convex converging lens 192, whose plan side 194 is oriented away from the beamsplitter. In first optics head 112a, emission light first may pass through an emission polarizer 132, as shown in Figure 5. Third lens 192 focuses the cylindrical portion 190 of emission light into a third cone of light 196 that impinges on emission fiber optic cable 134a for transmission to photoluminescence detector 144. To be transmitted by the fiber, the light should be focused onto emission aperture 131 at the tip 198 of the fiber as a spot comparable in size to the diameter of the fiber optic cable. Moreover, the incident cone angle θ_3 should not exceed the inverse sine of the numerical aperture of the fiber.

A property of the optical arrangement in top optics head 112a is that the tips 172, 198 of fiber optic cables 110a, 134a and the sensed volume of the composition are "confocal." Confocal means that all three objects are in conjugate focal planes, so that whenever one is in focus, all are in focus. The sensed volume of the composition lies in a focal or sample plane FP of the system, and the tips of the fiber optic cables lie in image planes IP of the

system. The detector also may be placed in an image plane, so that it detects the composition in focus. The tips of the fiber optic cables may be said to lie in intermediate image planes, because light passes through these planes, and the detector may be said to lie in a terminal image plane, because light terminates on the detector.

The sensed volume is created by placing confocal optics elements in or near one or more intermediate image planes. A preferred confocal optics element is an aperture. If such an aperture is placed in the excitation optical path, an image of the aperture will be focused onto the composition. As a result, only a portion of the composition within the focal plane corresponding to the shape and proportional to the size of the aperture will be illuminated, and only luminescent molecules in or near that portion of the focal plane will be induced to emit photoluminescence. If such an aperture is placed in the emission optical path, an image of the aperture will be focused onto the detector. Luminescence that ordinarily would focus onto a part of the detector outside the image of the aperture will be blocked or masked from reaching the detector.

The "shape" (or intensity profile) of the sensed volume depends on the confocal optics elements, such as excitation and emission apertures 116, 131, the light source, and the numerical apertures of the lenses and fiber optic cables. Generally, the intensity of the light incident on (or emitted from) the sensed volume will be greatest at the center of the sensed volume, and will decay monotonically in all directions away from the center. Most of the intensity will lie within a distance equal to about one aperture diameter from the center of the sensed volume in the Z direction, and within about one-half an aperture diameter from the center of the sensed volume in the X and Y directions.

Figure 7 also shows a sample container sensor switch 230, which is used to prevent damage to optics head 112a by preventing the optics head from physically contacting a sample container. Sample container sensor switch

230 is mounted about a pivot axis P adjacent chemiluminescence head 150. Sample container sensor switch 230 includes a sensor surface 232 positioned so that a sample container must contact the sensor surface before contacting any component of top optics head 112a. Contact between a sample container and sensor surface 232 causes sample container sensor switch 230 to pivot about pivot axis P, activating an electrical circuit that turns off power to the mechanism(s) used to move the sample container.

A sample container sensor switch is especially important in an analyzer designed for use with a variety of sample containers, because it reduces the likelihood of damage both from exotic sample holders with unusual dimensions and from standard sample holders with aberrant or misidentified dimensions. The sample container sensor switch may detect impending contact between the sample container and optics head (1) mechanically, as in the preferred embodiment, (2) optically, as with an electric eye, (3) acoustically, as with an ultrasonic detector, or (4) by other mechanisms.

Figure 7 also shows a chemiluminescence head 150, which includes a chemiluminescence baffle 152 and a chemiluminescence fiber optic cable 156. Chemiluminescence head 150 is mounted on top optics head 112a, but also could be mounted on bottom optics head 112b or on both top and bottom optics heads 112a,b.

Figure 8 shows an alternative embodiment of top optics head 112a, which includes an alternative embodiment of chemiluminescence head 150.

Figure 9 shows an alternative view of chemiluminescence head 150. In chemiluminescence, emission light sensitivity is maximized by detecting as much emission light as possible from the top of the sample container. In analyzer 50, this is accomplished by placing fiber optic cable 156 directly above and aligned with the center of the microplate well or other sample container. A high numerical aperture fiber optic cable may be used to collect most or substantially all of the light emitted from the composition. A

preferred fiber optic cable has a numerical aperture of 0.22 and is formed of silica for low autoluminescence.

Detection of chemiluminescence light further is enhanced by positioning fiber optic cable 156 so that the gap G or flying height between the fiber optic cable and the top of the sample container is as small as possible. Generally, if the gap between the top of the microplate and the fiber optic cable is small compared to the diameter of the fiber optic cable, most of the emission light will be collected. In analyzer 50, preferred values of G lie in the range 0.25-1.5 mm, depending on the type of microplate. The preferred values allow for normal variations in microplate thickness and minimize the possibility of contacting liquid that may be on the surface of the microplate. This is accomplished by accurate calibration of the travel of the optical head along the Z-axis relative to a reference point on the Z-axis. The height of various microplates can be stored in software so that G can be set by the instrument to a preselected value.

Gap G also can be determined empirically using a precision top-of-plate sensor, which is mounted on the bottom of the upper optics head. The height of the plate is measured by slowly moving the optics head toward the plate until the top-of-plate sensor indicates that a known flying height has been achieved. With this approach, the height of the plate need not be known in advance. Moreover, if a microplate mistakenly is inserted into the machine with a greater than expected height, the top-of-plate sensor can be used to prevent the optics head from colliding with the microplate.

Chemiluminescence head 150 also includes a chemiluminescence baffle 152, which supports fiber optic cable 156 and an aperture support slide 250 and which also minimizes detection of ambient light and chemiluminescence from neighboring wells. Detection from neighboring wells may be referred to as "cross talk." In analyzer 50, chemiluminescence baffle 152 is generally circular and includes a black surface 252 with rugosities 153 designed to absorb light. Chemiluminescence baffle 152 may have a diameter at

least about twice the diameter of the fiber optic cable, and may be configured to allow low cross talk to be achieved at comfortable flying heights.

Figure 10 shows a partially cross-sectional perspective view of chemiluminescence head 150. Chemiluminescence head 150 includes a fiber optic cable 156 and an aperture support plate 250 containing apertures 254a,b that determine an "effective" entrance diameter for the fiber optic cable. In turn, the effective entrance diameter for the fiber optic cable determines the size of the sensed volume within the sample. To maximize signal, apertures 254a,b generally are chosen substantially to equal the diameter of the microplate well. Large apertures 254a having diameters larger than fiber optic cable 156, and small apertures 254b having diameters smaller than fiber optic cable 156 may be placed in front of the fiber optic cable. A moveable aperture support slide 250 may include separate apertures for 96, 384, 768, 1536, 3456, and 9600 well plates, among others, where each aperture is optimized for the well size associated with a particular microplate. Alternatively, a fixed aperture support slide 250 may include a continuous iris diaphragm aperture, where the size of the continuous diaphragm may be optimized for a range of well sizes.

Alternative embodiments of the chemiluminescence optical system could include a plurality of chemiluminescence heads optically connected to a plurality of chemiluminescence detectors. The chemiluminescence heads could be mounted as a linear array or as a matrix. For example, a linear array of 8 or 12 chemiluminescence heads optically connected to 8 or 12 detectors could be used to detect simultaneously from entire rows or columns of a 96-well microplate. Moreover, the same arrays also could be used with the appropriate apertures to detect from higher-density plates in which the well-to-well spacing is evenly divisible into the well-to-well spacing in the 96-well plate, as for 384 and 1536-well plates. The chemiluminescence heads also could be mounted as a matrix that could detect from one or more plate formats.

Other alternative embodiments of the chemiluminescence optical system could include a plurality of fiber optic cables connected as a bundle to a CCD detector or to a PMT array. The fiber optic bundle could be constructed of discrete fibers or of many small fibers fused together to form a solid bundle. Such solid bundles are commercially available and easily interfaced to CCD detectors.

These alternative embodiments may be used with alternative embodiments of chemiluminescence baffle 152. For example, with a fiber optic bundle, cross-talk between wells within the matrix can be minimized by keeping G as small as possible and/or by applying an anti-reflective coating to the face of the fiber bundle. An anti-reflective coating can reduce reflected light from about 4% to less than 1%. In addition, a baffle having a rough black surface as described above could be placed around the outside of the fiber bundle, like a collar, to minimize pick-up from areas of the plate that are not under the bundle.

Figure 11 shows the relationship between top and bottom optics heads 112a,b and chemiluminescence head 150. Top and bottom optics heads 112a,b are coupled to an optics head support structure 260, which includes a gap 262 through which a stage and sample container can pass. Optics head support structure 260 is configured so that the relative positions of top and bottom optics heads 112a,b are fixed.

Figure 11 also shows a Z-axis adjustment mechanism 130, which is used to adjust the position of a sensed volume within a composition. Z-axis adjustment mechanism 130 includes a support track 264 that is substantially parallel to a Z-axis on which optics head support structure 260 is mounted. Z-axis adjustment mechanism 130 also includes a motor 266 for moving optics head support structure 260 along support track 264. The position of a sensed volume within a composition positioned in gap 262 is adjusted by moving top and bottom optics heads 112a,b relative to the composition. Movement relative to the composition may be effected by moving the optics heads while keeping

the composition stationary, as here, or by moving the composition while keeping the optics heads stationary, among other mechanisms.

Figure 11 also shows aspects of bottom optics head 112b. Generally, bottom optics head 112b resembles top optics head 112a. However, bottom optics head 112b includes a window 267 and an elevated drip lip 268 that are not included on top optics head 112a. Window 267 and drip lip 268 prevent fluid dripped from a microplate from entering bottom optics head 112b. Fluid dripped from a microplate is a concern with bottom optics head 112b because the bottom optics head is positioned below the microplate during analysis.

Figures 11 and 12 show further aspects of bottom optics head 112b. Generally, light is directed through bottom optics head 112b much like light is directed through top optics head 112a. However, light also may be directed by an alternative optical relay structure 269 to the bottom (or top) optics head. Alternative optical relay structure 269 may include a fiber optic cable 270 and focusing lens structure 271. Off-axis illumination eliminates loss of light due to absorption and reflection from the beam splitter and substantially eliminates reflection of incident light into the detection optics, reducing background. Off-axis illumination also may be used for total internal reflection illumination.

Figures 11 and 12 also show the relative positions of top and bottom optics heads 112a,b. Top and bottom optics heads 112a,b may be aligned, so that excitation light transmitted by one optics head can be detected by the other optics head, facilitating absorbance assays. A shutter may be positioned between the two optics heads to prevent light from one optics head from entering and exciting fluorescence from the other optics head during luminescence assays. Alternatively, top and bottom optics head 112a,b may be offset, so that light from one optics head cannot enter the other optics head. A small optical relay structure, such as a fiber optic cable, may be positioned

adjacent or as part of bottom optics head 112b to detect light in a top illumination and bottom detection mode.

Application of Sensed Volumes

The optical system described above, and the confocal optics elements in particular, allow detection of luminescence substantially exclusively from a sensed volume of a composition.

Figure 13 shows a standard microplate well 126 and an excitation light beam 186 as it illuminates the well. The standard well is cylindrical and may be characterized by a diameter D_w and a height H_w. Other wells may have other geometries and be characterized by other quantities; for example, a well could be square and characterized by a width and a height, or a well could be conical and characterized by a cone angle and a height. The interface between composition 120 and the air 272 is termed the meniscus 274 and may be convex, plan, or concave.

Excitation light beam 186 is focused by the optical system so that it is shaped much like an hourglass along the optical (Z) axis. This hourglass shape arises as the cone of excitation light formed by the optics passes through focus. The diameter D_B of the beam is smallest at the beam's waist 276, which corresponds to the focal plane, above and below which the beam diverges monotonically, making an angle θ_B with respect to the vertical or Z-axis. Values of D_B and θ_B depend on optical components of the analyzer and may be varied by changing these components. Generally, D_B and θ_B are inversely related. The distance between the bottom of the well and the beam waist is termed the focal (Z) height, H_z.

The shape of the sensed volume, indicated by stippling, may differ in directions parallel and perpendicular to the optical or Z-axis. Parallel to the Z-axis, the shape may be Lorentzian, among others. Perpendicular to the Z-axis, the shape may be Gaussian, or it may be a rounded pulse function, among others. A laser beam might give rise to a Gaussian, whereas a fiber optic bundle might give rise to a rounded pulse function. Generally, lower numerical

apertures will create sensed volumes shaped more like cylinders, whereas higher numerical apertures will create sensed volumes shaped more like hourglasses.

The shape and volume of the sensed volume may be adapted like a probe to match the shape and volume of the sample container. Thus, the sensed volume may be expanded for maximum signal in a large sample container, and contracted to avoid nearby walls in a small sample container. The shape and volume of the sample container also may be chosen or designed to conform to the shape and volume of the sensed volume.

Alternatively, the sensed volume may be held constant. In this way, the sensed volume will report on equal volumes of each composition analyzed, so that the analyzer effectively reports "intensive" quantities. Intensive quantities do not depend on the amount of composition in a sample container; in contrast, extensive quantities do depend on the amount of composition in the sample container. This approach can be used to facilitate comparison of results obtained from different-sized sample wells, such as in 96 and 384 well microplates. Alternatively, this approach can be used to facilitate comparison of results obtained from like-sized sample wells containing different volumes of solution, as by design or by error.

Figure 14 shows how the signal-to-noise and signal-to-background ratios are affected by focal height for two assay modes. In homogeneous assays (Panel B), photoluminescent molecules are distributed uniformly throughout the composition, and the optimum signal-to-noise and signal-to-background ratios are obtained regardless of well geometry when the sensed volume is positioned in the middle of the composition (Panel A), so that the sensed volume does not overlap with the meniscus or the bottom or sides of the well. If the meniscus is in the sensed volume, light reflected from the meniscus will be detected. This will decrease sensitivity by increasing background and decreasing signal. If the bottom of the well is in the sensed volume, light reflected from the well bottom will be detected. Moreover,

noncomposition photoluminescence arising from fluorescent and other photoluminescent materials that are commonly included in the microplate or adsorbed to the walls of the microplate also will be detected. These two effects will decrease sensitivity by increasing background and decreasing signal. Luminescence measured from the microplate walls will lead to spuriously high luminescence intensities and luminescence polarizations.

In cell-based assays (Panels C and D), photoluminescent molecules are concentrated in or near cells growing at the bottom of the well, and the optimum signal-to-noise and signal-to-background ratios are obtained when the sensed-volume is centered about the bottom of the well (Panel A). Such centering may be accomplished either using top optics (Panel C) or bottom optics (Panel D).

The shape and position of the sensed volume within the well are affected by (1) the meniscus, (2) the geometry of the microplate well, and (3) the geometry of the whole microplate.

Figure 15 shows how the meniscus affects the shape and position of the sensed volume. When there is no fluid and hence no meniscus, the beam has a nominal undistorted shape; see Panel A. The meniscus affects the sensed volume because light is refracted as it crosses the meniscus boundary between the air and the composition. Specifically, light passing from air (with its lower index of refraction) to the composition (with its higher index of refraction) bends toward the normal, as described by Snell's law. Here, the normal is the direction perpendicular to the surface of the meniscus at a given point. If the meniscus is everywhere perpendicular to the light beam, then light passing through the meniscus will not bend, and the beam will retain its nominal undistorted shape. For a converging beam, this will occur when the meniscus is appropriately convex; see Panel B. If the meniscus is more than appropriately convex, light will bend toward the middle of the well as it passes through the meniscus, and the sensed volume will be compressed and raised; see Panel C. If the meniscus is less than appropriately convex, flat, or concave, light will bend

away from the middle of the well as it passes through the meniscus, and the sensed volume will be stretched and lowered; see Panel D. Meniscus effects could be minimized by appropriately configuring microplate wells.

Figures 16 and 17 show how the geometry of the microplate well affects the position of the sensed volume. In particular, if the well is sufficiently narrow relative to the diameter of the beam or if the well is sufficiently deep relative to the angle made by the beam, then the light beam may impinge upon the top walls of the well. In these cases, setting the Z-height too low can reduce sensitivity (1) by decreasing the desired signal because less light enters the well, and (2) by increasing the background because the light beam illuminates the tops of wells. Many microplates are made from materials that are fluorescent or otherwise photoluminescent, and the instrument will detect this photoluminescence from materials at the tops of wells.

Figure 17 shows how the geometry of the microplate affects the position of the sensed volume. The analyzer is configured automatically to find the location of each well in a given microplate, beginning with well A1. The analyzer does this using stored parameters describing the dimensions (plate heights, interwell distances, etc.) of the particular microplate style. However, these microplate parameters are nominal values and do not account for unit-to-unit or lot-to-lot variations in microplate geometry. If there is a slight variation in interwell distance, the light beam can be off-center on some wells even though it is perfectly centered on well A1. This effect is termed cross-plate drift.

Cross-plate drift of fluorescence readings may increase as the instrument scans across the microplate as variations are compounded. Typically, drift will be worst at well H12, which is farthest from well A1. Such drift can be reduced by making the stage more accurate, by making the sample containers of a more consistent size, or by increasing H_Z, which will reduce the diameter of the beam and put it back into the well. The lattermost approach is shown for well G11.

Because beam position is a critical determinant of signal to noise, Z height must be appropriately maintained; Z height should be kept above a critical focal height, $H_{Z,Crit}$. The height at which the beam first impinges on the walls of the well is the critical focal height, $H_{Z,Crit}$. Figure 18 shows how $H_{Z,Crit}$ depends on the well height H_W and well diameter D_W, for a beam of diameter 1.5 millimeters (mm) and a beam angle θ_B of 12.7 degrees. Similarly, Table 1 shows how $H_{Z,Crit}$ depends on well height and well diameter for four commercially available microplates.

Plate Type	Well Height (mm)	Well Diameter (mm)	$H_{Z,Crit}$ (mm)
Costar Black Flat Bottom 96-Well 3915	10.71	6.71	-0.85
Dynatech MicroFluor Round Bottom	9.99	6.78	-1.72
Costar Black 384-Well 3710	11.55	3.66	6.76
Packard White 384-Well #6005214	11.57	3.71	6.67

Z-height can be optimized for a particular microplate and chemistry by (1) preparing a test microplate with representative chemistry (e.g., blanks, positive and negative controls, dilution series), (2) and reading the microplate multiple times at different Z-heights to determine the Z-height that gives the best signal-to-background data. Some combinations of chemistry and microplate are relatively insensitive to Z-height, while others demonstrate a distinct optimum.

As described above, a sample container sensor switch is mounted on the top optics head to prevent the plate from contacting the optics head in case the plate is misaligned, not properly specified, or the Z-height is set incorrectly. If this sensor detects a fault, the sample container will be ejected prior to reading.

Although this discussion was presented for microplates, the same principles apply with other sample containers.

Light Source and Detector Modules

Figure 19 is a perspective view of a light source module 400 employed in an embodiment of the invention. Portions of the module case have been removed to reveal internal componentry. Light source module 400 includes at least two light sources. A flashlamp 402 transmits light along a first light path 404. A second light source, namely, a continuous arc lamp (not shown) housed in compartment 406, transmits light along a second light path 408. A filter wheel assembly 410 is positioned adjacent the light sources. Filter wheel assembly 410 includes a filter wheel 412, which holds a plurality of filters 414. Filter wheel 412 is rotatable around an axis 416, so that a given filter can be positioned interchangeably along light path 404, or along light path 408, by rotating filter wheel 412. A fiber optic shuttle assembly 418 is mounted next to filter wheel assembly 410. Moveable shuttle 420 translates along support tracks 422a and 422b, so that moveable shuttle 420 can be positioned in front of a selected light source for a selected assay application. Two fiber optic ports 424 are provided on an external face of shuttle 420. Fiber optic ports 424 direct light, via fiber optic cables, from a selected source either to a top optics head or to a bottom optics head, above and below a stage holding a sample, respectively.

Figure 20 is a perspective view of an alternative light source module 426. In this embodiment, filter wheel assembly 410 of light source module 400 has been replaced by an alternative filter wheel assembly 427. A moveable shuttle 428 is shown in an alternative position relative to moveable shuttle 420 in light source module 400.

Figure 21 is a perspective view of a detector module 440 employed in an embodiment of the invention. Portions of the module case have been removed to reveal internal componentry. Detector module 440 is similar to light source module 400. A detector 442 receives light directed along a light path 444, originating from a sample. A filter wheel assembly 446 is positioned in front of detector 442. Filter wheel assembly 446 includes a plurality of filters

450 and is rotatable around an axis 451 by a stepper, DC servo, or other motor. The filter wheel can be rotated at a preselected angular speed to allow synchronization with a flash lamp light source and a detector. A port 452 for a second detector is provided in filter wheel assembly 446, so that a second detector can be mounted in detector module 440. A given filter in filter wheel 448 can be positioned along a first light path 444 leading to detector 442, or alternatively can be positioned along a second light path leading to a second detector (not shown). An attenuator mechanism 454 is mounted adjacent filter wheel assembly 446. A fiber optic shuttle assembly 456 is mounted in front of attenuator mechanism 454. Shuttle assembly 456 includes a moveable shuttle 458, which is moveable along upper and lower support tracks 460a and 460b, respectively. An exterior face of shuttle 458 has two fiber optic ports 462, one of which is connected, via a fiber optic cable, to a top optics head above the examination site, the other of which is connected, via a fiber optic cable, to a bottom optics head below the examination site. In operation, moveable shuttle 458 can be moved along support tracks 460a and 460b to connect optically either one of the optics heads to any one of the detectors (if more than one is included in the module), and through any one of filters 450 in filter wheel 448.

Figure 22 is a perspective view of an alternative detector module 466. In this embodiment, filter wheel assembly 446 of detector module 440 has been replaced by an alternative filter wheel assembly 467. A moveable shuttle 468 is shown in an alternative position relative to moveable shuttle 458 in detector module 440.

Light source and detector modules are designed for flexibility. Additional ports for fiber optics or other optical relay structures may be provided, if desired. The number and configuration of such other ports may be tied to the number and configuration of light-transmission routes through the filter wheel. Optical components also may be connected directly to the moveable shuttle. Such a connection would be especially useful for small, dedicated components, such as a beamsplitter and photodiode-type detector that

could sample a portion of the light transmitted through the port to correct for output fluctuations from a light source.

A comparison of Figures 19 and 21, and Figures 20 and 22, shows that many aspects of light source modules 400 and 426 and detector modules 440 and 466 are the same, particularly the mechanics of filter wheel assemblies 410 and 446, filter wheel assemblies 427 and 467, and fiber optic shuttle assemblies 418 and 456. The light source and detector modules both function as registration mechanisms that align the end of an optical relay structure with an aperture in a surface. This surface may enclose a light source, detector, or other optical component. The light source and detector modules both permit alignment with two such apertures, and with portions of a surface not including an aperture to prevent the optical relay structure from transmitting light. Light source and detector modules also may be configured to transmit light directly from module to module, using air, a tube, or other mechanism to transmit light. If used together in a light detection device, the light source and detector modules provide a great deal of analytical flexibility to select different combinations of light sources, detectors, and filters for different applications, while also being able to select different combinations of top versus bottom illumination and detection orientations.

Figure 23 is a partial perspective view of a fiber optic shuttle assembly 480 like those used in light source module 400 and detector module 440. Fiber optic shuttle assembly 480 includes a moveable shuttle 481 and two floating head assemblies 482. Among other applications, each floating head assembly 482 may be used to create and maintain a light-tight connection between selected light sources or detectors and fiber optic cables, such as those that lead to an examination site, or to a top optics head or a bottom optics head, above and below a stage, respectively.

Figure 24 shows a perspective view of a floating head assembly 483 employed in an embodiment of the invention. Generally, floating head assembly 483 includes a fiber optic ferule 484 having an end 485 configured to

transmit light, and an opaque collar 486 positioned around the end. Fiber optic ferule 484 is used to transmit light. Fiber optic ferule 484 may be replaced by a portion of a light source, detector, or other optical component. Opaque collar 486 is used to block light and preferably comprises a hard plastic material. Opaque collar 486 encompasses and extends beyond end 485. An opaque base structure 487 contains additional elements. Together, opaque collar 486 and base structure 487 form a pair of concentric, partially overlapping walls positioned around fiber optic ferule 484.

Figure 25 is a cross-sectional view of floating head assembly 483. A spring 488 is positioned between portions of opaque collar 486 and base structure 487. Spring 488 generally comprises any elastic body or other device that recovers its original shape when released after being distorted. Spring 488 is configured to spring-bias opaque collar 486 relative to end 485 when spring 488 is compressed between opaque collar 486 and base structure 487. Spring 488 bias pushes opaque collar 486 and base structure 487 in opposite directions parallel to a central axis 489 running through fiber optic ferule 484. A flange 490 on opaque collar 486 contacts a retaining ring 491 on base structure 487 when opaque collar 486 is maximally extended, limiting relative movement of opaque collar 486 and base structure 487. Additional or alternative stop mechanisms also may be employed, such as a set screw.

In use, floating head assembly 483 is positioned such that fiber optic ferule 484 is aligned with an aperture 492 in a surface 493, so that light may be transmitted between fiber optic ferule 484 and aperture 492. When end 485 and aperture 492 are aligned, a leading rim edge 494 of opaque collar 486 is spring-biased or forced against surface 493 by compression of spring 488. Leading rim edge 494 defines an end plane that is moveable relative to central axis 489. Opaque collar 486 and thus leading rim edge 494 automatically float or reorient relative to surface 493, forming a substantially light-tight junction by changing angle relative to central axis 489. This substantially light-tight junction substantially prevents stray light from entering the system, and it

substantially prevents signal light from exiting the system. Spring 488 is relatively more compressed where surface 493 is closer to floating head assembly 483 and relatively less compressed where surface 493 is farther from floating head assembly 483, so that contact between opaque collar 486 and surface 493 is maintained for different positions and/or orientations of surface 493. Portions of opaque collar 486 may be formed of a material that deforms under pressure from spring 488 to conform substantially to asperities or other irregularities in surface 493.

Figure 26 shows a perspective view of an alternative floating head assembly 495. Generally, alternative floating head assembly 495 includes a fiber optic cable 496 having an end 497 configured to transmit light, and an opaque collar 498 positioned around the end.

Figure 27 shows a cross-sectional view of alternative floating head assembly 495. Fiber optic ferule 496 and opaque collar 498 are supported by a base structure 499 that includes a spherical bearing 500 having an inner race 501 and an outer race 502. Inner race 501 is slidingly connected to a sleeve portion 503 of opaque collar 498 that extends along fiber optic ferule 496. Outer race 502 is connected to a platform structure 504 used for mounting alternative floating head assembly 495. A spring 505 is positioned between portions of opaque collar 498 and outer race 502. Spring 505 bias pushes opaque collar 498 and base structure 499 in opposite directions parallel to a central axis 490 running through fiber optic ferule 496. A retaining ring 507 prevents over-extension of opaque collar 498.

In use, alternative floating head assembly 495 is positioned, like floating head assembly 483, such that fiber optic ferule 496 is aligned with an aperture 508 in a surface 509, so that light may be transmitted between fiber optic ferule 496 and aperture 508. When so aligned, opaque collar 498 and fiber optic ferule 496 are free to compress and extend due to the action of spring 505, and to swivel and reorient due to the action of spherical bearing 500, relative to surface 509. The combined actions of spring 505 and spherical

bearing 500 ensure that central axis 506 of fiber optic ferule 496 always is substantially parallel to an aperture axis 510 running through aperture 508, unlike with floating head assembly 483.

Filter Wheel Assemblies

Figure 28 shows a partially exploded perspective view of an optical filter wheel assembly 520 employed in an embodiment of the invention. Optical filter wheel assembly 520 includes a filter wheel 521 that is rotatable about a hub structure 522, and a wheel case having a static base portion 523 and a removable lid portion 524. Hub structure 522 is built into removable lid portion 524.

Filter wheel 521 holds filter cartridges 525. Filter wheel 521 is substantially circular and includes a plurality of apertures 526 disposed symmetrically about its outer perimeter 527. Apertures 526 are used for mounting filter cartridges 525 and may hold the filter cartridges via friction, threads, or other means. Filter wheel 521 may have a variety of shapes, and apertures 526 may be disposed in a variety of configurations, although a symmetric embodiment is preferred for balance and ease of rotation about hub structure 522.

Removable lid portion 524 holds filter wheel 521. Removable lid portion 524 is substantially rectangular, with an enclosed top 528 and sides 529a-d and an open bottom 530 for receiving filter wheel 521. Opposed flanges 531 extend downward from one pair of opposed sides 529b,d of removable lid portion 524 to support hub structure 522. Filter wheel 521 is rotatably mounted through its center on hub structure 522.

Static base portion 523 holds removable lid portion 524 and filter wheel 521. Static base portion 523 is substantially rectangular, with an enclosed bottom 532 and sides 533a-d and an open top 534 for receiving filter wheel 521. Opposed slots 535 extend downward into one pair of opposed sides 533b,d of static base portion 523 to receive opposed flanges 531. Opposed posts 536 extend upward from the other pair of opposed sides 533a,c of static

base portion 523 to be received by opposed holes 537 in opposed sides 529a,c of removable lid portion 524. Flanges 531 and slots 535, and posts 536 and holes 537, individually and collectively form a post-to-hole mating structure that aligns static base portion 523 and removable lid portion 524 when the two portions are mated together to form the wheel case. Captive screws 538 situated in holes 537 and accessible from top 528 may be threaded into posts 536 to hold together removable lid portion 524 and static base portion 523. Static base portion 523 further may be fixed to an instrument platform to form a portion of a light source module, detector module, or other optical assembly, among other applications.

The assembled wheel case is substantially light-tight, except for light that is transmitted through two sets of opposed windows 539 included in static base portion 523. Windows 539 are used for transmitting light through the wheel case and through a selected optical filter contained in a filter cartridge 525 in filter wheel 521. Windows 539 are located on opposite sides of hub structure 522, so that any given optical filter in filter wheel 521 can be rotated into alignment with either set of windows. In turn, light sources, detectors, and other optical components can be aligned with either or both sets of filters. Generally, the wheel case includes at least one set of windows, which may be located on the static portion, removable portion, or other portion of the wheel case.

Filter wheel 521 may be rotated by a drive motor 540, which is attached to removable lid portion 524 in optical filter wheel assembly 520. Drive motor 540 or other driver mechanisms also may be operatively connected to optical filter wheel assembly 520 at other points and in other manners.

Figure 28 also shows a mechanism by which optical filter wheel assembly 520 may be disassembled and reassembled. Optical filter wheel assembly 520 is disassembled as follows. First, any associated instrument is powered down and unplugged. Second, any secondary housing enclosing optical filter wheel assembly 520 is removed. Third, drive motor 540 is

unplugged at its inline connector 541. Fourth, captive screws 538 are loosened. Finally, removable lid portion 524 and filter wheel 521 are pulled out of static base portion 523.

Optical filter wheel assembly 520 may be reassembled as follows. First, filter cartridges 525 are checked to verify that they are properly seated in filter wheel 521, and filter wheel 521 is checked to verify that it rotates smoothly about hub structure 522 when moved by hand. Second, removable lid portion 524 and filter wheel 521 are inserted into static base portion 523, aligning flanges 531 with slots 535, and posts 536 with holes 537. Third, captive screws 538 are tightened. Fourth, drive motor 540 is plugged back in at inline connector 541. Fifth, any secondary housing is replaced. Finally, any associated instrument is plugged back in and powered up, if desired.

Figure 29 shows a partially exploded perspective view of a removable portion 542 of an optical filter wheel assembly, including a filter wheel 543, removable lid portion 544, and drive motor 545. Filter wheel 543 includes a set of "short" filter cartridges 546 and a set of "tall" filter cartridges 547. Filter wheel 543 may hold a variety of filter cartridges, so long as the filter cartridges are configured to fit in apertures 548 in the filter wheel. Generally, opposed apertures in filter wheel 543 should contain matching filter cartridges or a suitable slug to balance the filter wheel and to prevent unfiltered radiation from reaching a detector.

Figure 29 also shows a mechanism by which short filter cartridges 546 may be removed and replaced. Generally, short filter cartridges 546 include an optical filter 549 permanently affixed by suitable means, such as glue, to a short filter barrel 550 having a low profile. Optical filter 549 may include an intensity filter, a spectral filter, or a polarization filter, among others. Short filter cartridges 546 are removed from filter wheel 543 as follows. First, with the filter wheel removed as described above, the desired short filter cartridge is located by sight or by location. (Filter cartridge locations within the filter wheel may be marked on the filter wheel or elsewhere for reference.)

Second, the short filter cartridge is removed by turning it counter-clockwise, which unscrews it. The short filter cartridge may be turned by hand or by a special tool, such as a spanner wrench 551 having prongs 552 that engage grooves 553 in the sides of the short filter cartridge 554. Finally, filter changes are noted on the filter wheel or elsewhere and in any associated instrument software. Short filter cartridges 546 may be replaced in filter wheel 543 by reversing the process, turning the short filter cartridge clockwise.

Figure 30 shows a partially exploded perspective view of a removable portion 555 of an optical filter wheel assembly, as shown in Figure 29. Figure 30 also shows a mechanism by which tall filter cartridges 556 may be removed and replaced. Generally, tall filter cartridges 556 include an optical filter 557 affixed by a removable friction member 558 to a tall filter barrel 559. Optical filter 557 may include an intensity filter, a spectral filter, or a polarization filter, among others. Friction member 558 and tall filter barrel 559 may be substantially annular. Tall filter cartridges 556 may be removed from and replaced in filter wheel 560 much like short filter cartridges 546; however, tall filter cartridges 556 generally are turned by hand rather than by a tool.

Figures 31 and 32 show a perspective view of a mechanism by which optical filters may be replaced in the tall filter cartridges. First, as shown in Figure 31, the optical filter 561 is placed in the tall filter barrel 562. Optical filter 561 should be oriented properly if one side is different than the other. Additional optical filters 561 can be placed in tall filter barrel 562, if desired. Second, as shown in Figure 32, a funnel structure 563 is placed on top of tall filter barrel 562. Third, an annular friction member 564 is placed in funnel structure 563, followed by a slug 565. Slug 565 and optical filter 561 have approximately equivalent peripheral dimensions, including radii. Fourth, slug 565 is pushed down through funnel structure 563 to compress friction member 564, which should fit snugly against optical filter 561. Finally, slug 565 and funnel structure 563 are removed. The completed tall filter cartridge then can be installed in a filter wheel, as described above.

Optical filter 561 also may be replaced by other techniques. Generally, the tall filter cartridges incorporate a mechanism that permits easy replacement of different optical filters in the same cartridge, enhancing the flexibility of the tall cartridges.

Optical filter 561 may be removed from the tall filter cartridge as follows. First, a lint-free cloth is placed on a work surface. Second, the installed optical filter 561 (or slug 565) is pushed gently near its center with a gloved finger or thumb, which will cause the optical filter 561 and friction member 564 to drop out of tall filter barrel 562. Removed optical filter 561 should be stored so that it will not become dirty or scratched.

Figures 33 and 34 show detailed views of a short filter cartridge 566, which includes a short filter barrel 567 and optical filter 568. Short filter barrel 567 is substantially annular, with a threaded lower portion 569 that screws into an aperture in a filter wheel, and a graspable upper portion 570 having a knurled rim 571 that may be turned by hand. Optical filter 568 is supported by upper portion 570, and mounts adjacent a stop structure 572 and inner wall 573 on short filter barrel 567, so that it is substantially centered relative to short filter barrel 567. Stop structure 572 includes an edge 574 oriented substantially perpendicular to a principal plane of optical filter 568 and to inner wall 573.

Figures 35 and 36 show detailed views of a tall filter cartridge 575, which includes a tall filter barrel 576 and optical filter 577. Tall filter cartridge 575 resembles short filter cartridge 566 in many respects. Tall filter barrel 576 is substantially annular, with a threaded lower portion 578 that screws into an aperture in a filter wheel, and a graspable upper portion 579 having a knurled rim 580 that may be turned by hand. Optical filter 577 is supported by upper portion 579, and mounts adjacent a stop structure 581 and inner wall 582. Stop structure 581 includes an edge 583 oriented substantially perpendicular to a principal plane of optical filter 577 and to inner wall 582. Inner wall 582 may be substantially perpendicular to the optical filter, as here,

or it may have a funnel portion that graduates in diameter in a direction toward the stop structure, among other configurations. Lower portion 569 of short filter barrel 567 is substantially identical to lower portion 578 of tall filter barrel 576. However, upper portion 570 of short filter barrel 567 is shorter than upper portion 579 of tall filter barrel 576, giving it a lower profile. In addition, optical filter 568 of short filter barrel 567 is permanently affixed to upper portion 570, whereas optical filter 577 of tall filter barrel 576 is removably sandwiched in upper portion 579 between stop structure 581 and a friction member 584. Friction member 584 holds optical filter 577 in place relative to inner wall 582 in tall filter cartridge 575 by static friction, without any thread, groove, or adhesive. For this reason, among others, optical filters of various numbers and sizes may be secured.

Friction member 584 may take a variety of forms, including a compressible ring having an uncompressed outer diameter greater than the inner diameter of inner wall 582. The compressible ring may exert a force on the inner wall that provides sufficient static friction to hold an optical filter snugly in place during routine use, while also permitting easy removal when replacing optical filters.

Figures 37 and 38 show detailed views of a funnel structure 585, which is used for loading an optical filter into a tall filter cartridge or other holder as described above. Funnel structure 585 is substantially annular and includes inner and outer walls 586, 587 and a top end 588 and lower edge 589. Lower edge 589 includes a groove 590 adjacent inner wall 586 configured to rest on top of a filter cartridge or other holder. The inner diameter of funnel structure 585 measured between inner walls 586 enlarges gradually in a direction from lower edge 589 to top end 588.

Figure 39 shows a perspective view of a pivotable filter cartridge 592. Pivotable filter cartridge 592 includes a pivot aperture 593 and filter apertures 594. Pivot aperture 593 is used to receive a drive axle or other pivot structure. Filter apertures 594 are used to hold optical filters, which may be

secured to pivotable filter cartridge 592 using glue, short or tall filter cartridges, or other means. Generally, pivotable filter cartridge 592 resembles a spoke portion of a filter wheel and includes only one or a few optical filters disposed around a portion of a circle. Pivotable filter cartridge 592 may be used for moving an optical filter in and out of an optical path, much like a filter wheel or filter slide, by rotating pivotable filter cartridge 592 about a pivot axis running through pivot aperture 593. Because pivotable filter cartridge 592 may move one or a few filters in an out of an optical path by rotating through a limited angle, it may be configured to require less space that a filter wheel of comparable radius. In analyzer 50, pivotable filter cartridge 592 may be used to secure polarization filters, intensity filters, or other optical components.

Stage

Figures 40-43 show a stage, which generally comprises any mechanism for supporting a composition for analysis by the analyzer. In analyzer 50, the stage takes the form of a transporter 600.

Transporter 600 includes a transporter body 602 and substantially parallel first and second transporter flanges 604a,b that extend outward from transporter body 602. First and second transporter flanges 604a,b terminate in first and second transporter extensions 606a,b that turn in toward one another without contacting one another. Transporter body 602, flanges 604a,b, and extensions 606a,b lie substantially in a plane and define a transporter cavity 608 that is larger than any sample containers which the transporter is intended to support. The shape of this cavity is chosen to accommodate the shape of the preferred sample containers. In analyzer 50, cavity 608 is substantially rectangular to accommodate substantially rectangular sample containers, such as microplates. In analyzer 50, long sides of the rectangular sample container are positioned against flanges 604a,b.

Transporter shelves 610 along portions of body 602, flanges 604a,b, and extensions 606a,b form a structure that supports the bottom of the

sample container. Other support mechanisms, such as pins or pegs, also could be employed instead of, or in addition to, shelves.

The transporter also includes an automatic sample container positioning mechanism 620 for precisely and reproducibly positioning sample containers within the cavity 608. Mechanism 620 includes Y and X axis positioning arms 622a,b that contact the sample container to control its Y and X position, respectively. Here, a Y axis is defined as generally parallel to transporter flanges 604a,b, and an X axis is defined as perpendicular to the Y axis and generally parallel to transporter extensions 606a,b. Other coordinate systems also can be defined, so long as they include two non-colinear directions.

Y-axis positioning arm 622a lies substantially within channel 624 in body 602. Y-axis positioning arm 622a includes a rod 626a, which is bent at substantially right angles to form three substantially coplanar and equal-lengthed segments. A first end segment 628a of rod 626a terminates near cavity 608 in a bumper tab 630a for engaging a sample container. First end segment 628a is inserted into a bumper 632. A second end segment 634a of rod 626a terminates away from cavity 608 in an actuator tab 636a for controlling movement of arm 622a. Actuator tab 636a is bent away from body 602. First and second end segments 628a, 634a are substantially parallel. A middle segment 638a of rod 626a connects the two end segments at their non-tabbed ends 640, 641. An X-axis biasing spring 642a is slipped over rod 638a and a first spring end 644 is held to second end segment 634a of rod 626a by a clamping-type retaining ring 670a. A second spring end 648 rests against the rod bearing 671. The Y-axis biasing spring extends substantially parallel to first and second end segments 628a, 634a. The force from spring 642a is transmitted to rod 626a by the clamping action of retaining ring 670a.

X-axis positioning arm 622b also lies substantially within channel 624 in body 602 and is similar to Y-axis positioning arm, except that (1) first end segment 628b is longer and middle segment 638b is shorter in rod 626b of

the X-axis positioning arm than in rod 626a of the Y-axis positioning arm, (2) first end segment 628a terminates in a lever tab 630b in the X-axis positioning arm rather than in the bumper 632 in the Y-axis positioning arm, and (3) the two rods bend in opposite directions between the first end segments 638a,b and second end segments 634a,b.

X-axis positioning arm 622b is connected via lever tab 630b to an X-axis positioning lever 654 that lies along one of the transporter flanges 604b. X-axis positioning lever 654 includes two functional lever projections 656, 658 and is pivotally mounted about a lever pivot axis 659 to transporter 600 near the intersection of body 602 and flange 604b. A first lever projection 656 is substantially perpendicular to flange 604b and abuts lever tab 630b on X-axis positioning arm 622b for actuating the positioning lever. A second lever projection 658 also is substantially parallel to flange 622b and includes an edge 660 for contacting a sample container.

Transporter 600 functions as follows. For loading, the transporter occupies a loading position substantially outside a housing, as shown in Figure 44. In this position, actuator tabs 636a,b abut actuator bar 670, biasing springs 642a,b are compressed, and bumper 632 and second projection 658 having edge 659 are pulled out of cavity 608. A person, robot, or mechanical stacker then can place a sample container into cavity 608 so that the bottom of the sample container rests on shelves 610. Cavity 608 is larger than the sample container to facilitate this placement and to accommodate variations in sample container size.

For reading, the transporter must deliver the sample container to an examination site inside the housing. In this process, the transporter moves parallel to second end segments 634a,b and actuator tabs 636a,b disengage actuator bar 670. Biasing spring 642a pushes Y-axis positioning arm 622a toward cavity 608. Bumper 632 engages the sample container and pushes it away from body 602 until it abuts extensions 606a,b. Biasing spring 642b pushes X-axis positioning arm 622b toward cavity 608. Edge 659 of second

projection 658 engages the sample container and pushes it away from flange 604b until it abuts flange 604a.

Under the action of both positioning arms, the sample container is precisely and reproducibly positioned (registered) against a reference corner 672 within cavity 608. Biasing springs 642a,b can be chosen to have different strengths, so that the X-Y positioning action is performed less or more forcefully. In analyzer 50, middle segment 638b and first lever projection 656 of positioning lever 654 can be varied in length to cause registration to occur first in the X-axis or first in the Y-axis. For example, reducing the length of middle segment 638b and reducing the length of projection 656 will cause registration to occur first in the X-axis.

As long as the microplate is placed in any position on the lower guide shelves, it can be adjusted into place by the automatic microplate positioning mechanism. A sensor (not shown) detects the presence of the sample container. The instrument can be configured automatically to read the microplate once the sensor detects its presence, or the instrument may be configured to signal the system controller through the RS-232 port that a microplate has been received and that the instrument is ready to accept a command to begin reading.

Positioning lever 654 and bumper 632 are retracted when body 602 of the automatic microplate positioning transporter is moved to the eject position by the X,Y stage. Thus, the microplate is placed on the guide shelf 610 only when the lever and bumper are retracted. Two springs 642a,b are attached to the rods, which run along the length of the transporter body and end perpendicular to the body. When the transporter is moved to the eject position, the two perpendicular ends of the rods encounter a stop 670, which consists of a rectangular structure located above and parallel to the body. The stop prevents the two perpendicular ends of the actuators, and thus the actuators, from moving with the transporter body. This causes the two springs to contract, changing the position of the transporter arms and increasing the amount of

room for the microplate. The microplate can then be placed on the guide shelf of the body. When the body of the automatic microplate positioning transporter is moved back away from the stop, the two perpendicular ends of the actuators are no longer blocked, which allows the actuators, springs, and transporter arms to move into their original position. The expansion of the springs pushes the microplate into the exact position as defined by the reference corner.

Figure 43 shows a perspective view of transporter 600 mounted on base platform 700 with drive mechanisms for moving transporter 600 between loading and examination positions or sites. As previously described, transporter 600 includes flanges 604a,b defining cavity 608 for receiving and gripping a microplate (not shown). A drive mechanism is provided for moving transporter 600 along a track 702, relative to the Y-axis, from a loading position 704 toward an examination position 706. Once transporter 600 reaches the examination position, an additional drive mechanism can be actuated to move transporter 600 to the examination position along track 708 relative to the X-axis.

In operation, a microplate is loaded in transporter 600 at the loading position. Transporter 600 is driven toward the examination position by the Y-axis drive mechanism. The X- and Y-axis drive mechanisms then operate together to align selected microplate wells with the Z-axis, along which a sensed volume is defined by optical components contained in one or both of top and bottom optics heads positioned above and below base 700, respectively.

The X- and Y-axis drive mechanisms are controlled by a high-performance motion control system that maximizes throughput while minimizing detection errors. The control system includes precision five-phase stepper motors that employ encoder feedback to move the microplate quickly and accurately to each read position. The control system optimizes the acceleration/deceleration profiles of the microplate to minimize shaking of fluid within the microplate. This optimization is accomplished by minimizing "jerk" (the time rate of change of the acceleration of the microplate). Alternatively,

throughput may be increased if higher variation in results due to increased shaking and settling time may be tolerated.

Exterior Features

Figure 44 shows a high-throughput luminescence analyzer 50 constructed in accordance with the invention. Components of the analyzer are maintained in a housing 800, both for organization and for protection. Housing 800 is substantially rectangular and includes light-tight exterior top 802, side 803a-d, and bottom walls 804 that reduce background in luminescence measurements. The walls may include vents 806 to facilitate air flow through the analyzer and a transporter port 807 for sample input/output. Housing 800 also may include feet 808 to support the analyzer and to permit air flow between the analyzer and any support structure on which the analyzer is placed.

Analyzer 50 is substantially automated. The analyzer is designed so that user interactions occur primarily through a control unit 810, an electronic input/output panel 812, and a break-out box (not shown), each of which supports a variety of input/output functions. The analyzer also is designed so that sample input/output occurs primarily through a transporter/stage 814 and an optional sample feeder 816.

Control unit. Control unit 810 generally comprises any interface used for direct input/output functions. The control unit may be integrated into the analyzer, or it may be a separate unit that can be positioned away from the analyzer or affixed to the analyzer at one or more locations. The control unit also may include more than one unit, each dedicated to different input/output functions or to use at different locations.

The control unit 810 may be used in conjunction with a host computer for a variety of input/output functions. For example, the control unit may be used to input commands, such as signals to start and stop the instrument. Similarly, the control unit may be used to display output information, such as instrument status, instrument diagnostics, measurement results, and other information generated by the analyzer in different assay

modes. The control unit is especially useful for automated operations that require manual user intervention.

Figure 45 shows an enlarged isolated view of control unit 810 of analyzer 50. Control unit 810 is a separate unit that statically or swivelably affixes to the analyzer at any one of a plurality of docking locations. Control unit 810 is substantially L-shaped, with substantially perpendicular inner surfaces 830a,b that mate with adjacent substantially perpendicular walls of the analyzer including top wall 802 and one of side walls 803a-d, although other shapes are possible. In its preferred orientation, control unit 810 is mounted so that front face 832 is substantially parallel with one of side walls 803a-d of analyzer 50.

Control unit 810 includes various data input and output components. Front face 832 includes a gas-plasma display 834, keypad 836, and indicator lights 838. Control unit 810 also may include additional and/or alternative components, and their relative organization may deviate from that shown in the drawings and discussed below. Gas-plasma display 834 is located in the upper center of front face 832 and is used to provide messages regarding instrument status. Additional displays and/or alternative display formats, such as light-emitting diodes (LEDs) and liquid crystal displays (LCDs), also may be used.

Keypad 836 is located below and to the right of gas-plasma display 834 and includes four keys. A "start" key 840 initiates the sample-reading process. A "load/eject" key 842 loads or ejects a sample container, such as a microplate, depending upon the current status of the instrument. A "reset" key 844 reinitializes the instrument, sending motors to their home positions and turning off the audible alarm. A "status" key 846 alters the state of a continuous light source or activates reverse stack. Additional keypads and additional and/or alternative keys also may be employed. Alternative methods of data entry, such as a computer mouse or touch screen, also may be employed.

Indicator lights 838 are located to the left of the display and keypad. A "power" light 848 indicates that power is being supplied to the instrument. A "service" light 850 indicates that a service procedure is needed, such as changing a light source. A "fault" light 852 indicates that a critical fault has occurred, which is a fault that requires intervention by an operator. Additional and/or alternative indicator lights also may be provided.

Control unit 810 also may include audio signals. For example, an audible alarm within the interior of control unit 810 may sound in the event of a critical fault. Alternative audio signals, such as prerecorded or synthesized voice messages, also may be used.

Control unit 810 may be moved between at least two control interface docking-panel mounting locations 854a,b on the instrument. A first docking location 854a is located near an upper edge of sample input side 803b of housing 800. This configuration is especially suitable for manual operation, because control unit 810 and transporter port 807 are positioned on the same side of analyzer 50. A second docking location 854b is located near an upper edge of back side 803d of housing 800. This configuration is especially suitable for robotic operation, because control unit 810 and transporter port 807 are positioned on opposite side of analyzer 50, facilitating robotic access to transporter port 807. Such flexible positioning permits commands to be entered and status information, diagnostic information, measurements, and other information to be read from multiple positions. Flexible positioning is especially convenient when one or more sides of the analyzer are blocked due to analyzer placement or nearby peripherals. Alternatively, it permits two or more control units to be connected at once, increasing convenience and flexibility.

Figure 46 shows a control interface docking location 860. Control unit 810 includes an electronic connector prong, which can be mated with an electronic connector port 862 at docking location 860. Electronic connector port 862 is connected to a host computer, allowing the computer to

communicate with the control unit, so that a user can control the analyzer by inputting information through the control unit. Electronic connector port 862 preferably includes an RS-232 serial port, and preferably is connected to the host computer through an RS-232 cable. Control unit 810 also includes other mating structure, including substantially cylindrical prongs that match with receptors 864 and latches 866, and indentations that match with dimples 868, at docking location 860. Positioning docking location 860 at sites 854a,b on top wall 802 of housing 800 reduces the stress on the mating structure when the control unit is mounted; however, docking location 860 also can be positioned at other sites on or off housing 800.

Input/output panel. The input/output panel generally comprises any ports used for basic input/output functions. These include ports for providing and controlling power input to the analyzer, and for inputting and outputting data and commands. Components of the input/output panel may be collected for convenience in one location or positioned at various locations on the analyzer.

Figure 47 shows an enlarged isolated view of control input/output panel 812. In analyzer 50, input/output panel 812 includes a power switch 870, power entry module 872, auxiliary port 874, and two RS-232 serial ports 876. Power switch 870 is located in the left center of the panel and is used to actuate analyzer 50. Power entry module 872 is located below the power switch and is used to supply power to analyzer 50; power arrives via a standard electrical cord 878 that may be plugged into a wall socket. Auxiliary port 874 and serial ports 876 are located above and to the right of the power entry module and are used for input/output. These ports provide flexibility, because they permit the analyzer to communicate with several different peripherals. Additional power entry modules and additional and/or alternative communication ports for input/output in alternative formats and positions also may be used. A model/regulatory label 880 containing written information regarding the analyzer is provided below power entry module 872 on the input/output panel.

Break-Out Box. The analyzer also may include an external "break-out" accessory box connected to the instrument with a cable. The break-out box may include a connection block that allows the analyzer to provide a general purpose and hard-wired electrical interface to external devices, such as lamps, warning alarms, enunciators, associated instruments, and external system controllers. Through the break-out box, the instrument's software can be programmed to send or receive control signals from external systems or to control or provide signals to external devices. These control signals can be conditioned on the occurrence of predetermined internal events, such as when the analyzer finishes reading a plate or when a fault such as a mechanical jam occurs. Through the break-out box, the instrument also can accept signals from external devices or controllers to start reading a plate or perform other programmable functions.

Sample feeder

The analyzer may include a sample feeder, which generally comprises any mechanism for automatic processing of multiple sample containers. The sample feeder enhances convenience by reducing the amount of human intervention required to run the analyzer. The sample feeder also enhances throughput by reducing the amount of time required to process multiple microplates.

Generally, microplates conform to an approximate standard originally established for 96-well plates. Such a standard has been published by the Society for Biomolecular Screening; however, this standard has not been adopted universally within the industry. Because there is no exact standard for the size, shape, and construction materials used in microplates and because users may employ any number of commercially available or custom microplates for their applications, the feeder singulation mechanism should be able to perform the singulation operation with the widest possible range of microplate formats.

The present invention includes a mechanism capable of singulating a microplate or other container from a stack in the down-stacking or in-feed operation. This mechanism has inherently low sensitivity to the exact size, shape, construction material, and surface finish of the microplate. The invention may include four inwardly sloping, tapered (or angled) latches that cause the stack of plates to self-center within the plate input area to accommodate both relatively small and large plate sizes. The invention also may include a feature that causes the plates to drop gently when the singulation mechanism disengages from the edges of the plate, thus allowing the plate to drop onto the elevator mechanism support structure, which lowers the plate to the translation carriage without spilling fluid from the wells.

The down-stacking latches pivot on pins and are actuated by the elevator mechanism so as to retract when the elevator mechanism rises, thus releasing the bottom plate from the stack and allowing it to drop softly onto the elevator. When the latches retract, they pivot on their support pins such that their centers of gravity are offset. Consequently, when the elevator mechanism is lowered, the latches will be activated by gravity to return to their non-retracted or extended state, thereby preventing the next plate in the stack from dropping as the elevator mechanism is lowered. Because the offset in the center of gravity of the latches is only enough to cause them to return to their extended position, they press only very lightly on the edges of the microplate as it drops. Because the ends of the latches are polished smooth, they exert only a small frictional force on the edges of the plate so as not to cause the plate to cock or otherwise hang up as the elevator mechanism is lowered and the plate is placed on the translation carriage.

The translation carriage transports the microplate from the down stacking areas to the microplate reader's plate gripper, which, after a transfer operation, transports the plate to the interior of the plate reader where it is optically scanned. After scanning, the plate is transferred back to the translation carriage whereupon it is taken to the up-stacking or output area. The elevator

mechanism then raises the microplate by a fixed amount, thus causing it to pass by four spring-loaded latches, which are caused to retract as the plate is raised by the elevator. Once the bottom of the plate is above the top of the latch, the latches are released and a spring on each latch causes the latch to extend under the plate. The elevator mechanism then is lowered, causing the plate to be captured by the now extended latches. The up-stacked plate is thus added to the bottom of the output stack.

As shown in Figure 44, sample feeder 890 is integrated into the analyzer. Sample feeder 890 includes an input bin 892 for holding microplates to be read, an output bin 894 for holding microplates that have been read, and a direct transporter access bin 896 to input or output microplates by bypassing the input and output bins. Input and output bins 892, 894 accommodate input and output microplate magazines (not shown) that hold and organize stacks of microplates before and after reading, respectively. Microplate magazines can be used with other robotics to dispense, wash, and read without restacking microplates. Direct transporter access bin permits a user to access the transporter to deliver or remove a microplate without removing the magazines.

Sample feeder 890 operates as follows. Before reading, a robot (1) removes a microplate from the bottom of the stack of microplates in the input bin, (2) transports the microplate to the direct transporter access bin, and (3) transfers the microplate to the transporter. After reading, the robot (1) takes the microplate from the transporter, (2) transports the microplate to the output bin, and (3) transfers the microplate to the bottom of the output stack in the output bin.

Sample feeder 890 is designed to be flexible. Input and output bins 892, 894 can accommodate a variety of commercially available microplates and microplate magazines and are large enough to allow microplates to be placed in them by a robot. Suitable microplates typically have 96 or 384 wells, but other configurations also can be accommodated. Preferred 96-well microplates include COSTAR black flat-bottom model #3915 and

DYNATECH MicroFluor round-bottom model #_____; preferred 384-well microplates include COSTAR black model #3710 and PACKARD white model #6005214. Suitable microplate magazines can accommodate 10-100 microplates. Figure 44 shows magazines that can accommodate 20 microplates. Preferred microplate magazines include the TITERTEK S20 magazine.

Sample feeder 890 includes a process compression feature that reduces the number of passes that the robot must make to load and unload microplates on the transporter. This feature exploits the separate input (landing) and output (pickup) positions. The robot can pick up microplates that have been read from and place them in the output bin. microplates can be loaded into the direct transporter access bin by the robot and then the robot can go directly to the output bin to pick up the next microplate. Thus, one robot movement with the process compression feature replaces two separate robot movements without the feature. Finally, the automatic sample feeder requires only two motors to provide all mechanical functions with high throughput (~5 seconds for load and unload time). The robot can deposit a microplate in the input stack or the transporter and pick up a microplate after it is read from either the transporter or from the output stack.

In robotic operation, the feeder can reduce robot hand travel by providing separate landing (input) and pickup (output) positions. The system is designed to allow a microplate to be inserted and another removed by a robot in one pass, a feature known as Process Compression.

Sample feeder 890 may include a barcode reader 898 that can be used automatically to identify labeled microplates. Barcode reader 898 can be placed in either of the positions shown in boxes in dashed lines in sample feeder 840. Barcode reader 898 reads barcodes mounted on the long edge or the short edge of microplates. Barcodes are read while the feeder moves the microplate from the input magazine into the light-tight enclosure. Barcodes cannot be read when microplates are delivered directly to the transfer position. Barcode reader 898 can be programmed to decode a variety of symbologies,

including SPC (EAN, JAN, UPC), Code 39 (3-43 digits), Codabar (3-43 digits), Standard 2 of 5 (3-43 digits), Interleaved 2 of 5 (4-43 digits), Code 93 (5-44 digits), and MSI-Plessey (4-22 digits), among others. Information obtained from the barcode can be used for a number of different purposes. For example, the barcode string can be used to name the report file. The barcode can also be used to convey instructions to the analyzer relating to required changes in assay mode or optics configuration.

Generally, microplates conform to an approximate standard originally established for 96-well plates. Such a standard has been published by the Society for Biomolecular Screening; however, this standard has not been adopted universally within the industry. Because there is no exact standard for the size, shape, and construction materials used in microplates and because users may employ any number of commercially available or custom microplates for their applications, the feeder singulation mechanism should be able to perform the singulation operation with the widest possible range of microplate formats.

The present invention includes a mechanism capable of singulating a microplate or other container from a stack in the down-stacking or in-feed operation. This mechanism has inherently low sensitivity to the exact size, shape, construction material, and surface finish of the microplate. The invention may include four inwardly sloping, tapered (or angled) latches that cause the stack of plates to self-center within the plate input area to accommodate both relatively small and large plate sizes. The invention also may include a feature that causes the plates to drop gently when the singulation mechanism disengages from the edges of the plate, thus allowing the plate to drop onto the elevator mechanism support structure, which lowers the plate to the translation carriage without spilling fluid from the wells.

The down-stacking latches pivot on pins and are actuated by the elevator mechanism so as to retract when the elevator mechanism rises, thus releasing the bottom plate from the stack and allowing it to drop softly onto the

elevator. When the latches retract, they pivot on their support pins such that their centers of gravity are offset. Consequently, when the elevator mechanism is lowered, the latches will be activated by gravity to return to their non-retracted or extended state, thereby preventing the next plate in the stack from dropping as the elevator mechanism is lowered. Because the offset in the center of gravity of the latches is only enough to cause them to return to their extended position, they press only very lightly on the edges of the microplate as it drops. Because the ends of the latches are polished smooth, they exert only a small frictional force on the edges of the plate so as not to cause the plate to cock or otherwise hang up as the elevator mechanism is lowered and the plate is placed on the translation carriage.

The translation carriage transports the microplate from the down stacking areas to the microplate reader's plate gripper, which, after a transfer operation, transports the plate to the interior of the plate reader where it is optically scanned. After scanning, the plate is transferred back to the translation carriage whereupon it is taken to the up-stacking or output area. The elevator mechanism then raises the microplate by a fixed amount, thus causing it to pass by four spring-loaded latches, which are caused to retract as the plate is raised by the elevator. Once the bottom of the plate is above the top of the latch, the latches are released and a spring on each latch causes the latch to extend under the plate. The elevator mechanism then is lowered, causing the plate to be captured by the now extended latches. The up-stacked plate is thus added to the bottom of the output stack.

Figure 48 shows sample feeder 890 with bins 892 and 894 removed so that internal mechanisms can be viewed. Microplate 949 is loaded from the stack into first station 950. Microplate 949 is then transported on a tray (not shown) to station 952 where the microplate is handed off to a gripper (not shown). The gripper transports microplate 949 in the direction of arrow 953 to an examination site inside the analyzer. After analysis, microplate 949 is transported back to the second station 952, and then to third station 954 where

the microplate is added to the bottom of a stack of microplates in the output bin. In first station 950, a combination of two lifters and four latches cooperate to singulate or pick a single microplate from the bottom of a stack. In Figure 48, the lifters in first station 950 are concealed by microplate 949. Latches 958 have pick portions that extend into the cavity of station 950 and support a stack of microplates. Latches 958 are disposed toward the microplates by configuring the latch to have a center of gravity above and inward relative to a pivot point. As the lifters are raised in the first station, the pick portions of the latches are pushed out of the way so that the microplate can be supported and lowered by the lifters. After one plate has passed, latches 958 move back into a supporting position relative to the remainder of the stack.

A different latch configuration is employed in the output station 954. Latches 960 are urged inward toward the microplates by a spring (not shown). When lifter 962 lifts a microplate against latches 960, the microplate pushes the latches out of the way until the microplate is above the latch. Latches 960 then move back into a supporting position relative to the stack.

Figure 49A is a cross-section through infeed station 950. Lifters 970 have moved up through holes in tray 972 to contact the bottom of microplate 949, and in the process have pushed latches 958 out of the way. Figure 49B shows the same structures as in Figure 49A except that lifters 970 have dropped, thereby lowering microplate 949 onto tray 972 for transport to the analyzer. Pick portions of latches 958 have moved back into the cavity to support the remainder of the stack.

Similarly, in Figure 50A, microplate 949 is delivered to outfeed station 954 after analysis. Lifters 962 then move through holes in tray 972 to raise microplate 949 toward a stack of microplates in the outfeed bin (not shown). Figure 50B shows microplate 949 after the lifters have raised microplate 949 past latches 960. Latches 960 are spring biased toward the cavity of station 954. As lifters 962 raise microplate 949, latches 960 are pushed out of the way by the outer contour of microplate 949. Once microplate

949 is above latches 960, the latches return to their inward position to support the stack of microplates in the outfeed bin. Lifters 962 then retreat downward completely out of the holes in tray 972 so that tray 972 can translate back to infeed station 950 to collect another microplate for delivery to the analyzer.

Analyzer Set-Up, Calibration, and Reading

Operation of the analyzer includes set-up, calibration, and reading. Setup of the analyzer includes selection of an assay mode and selection of optical components and conditions to optimize performance in that assay mode. Selection of optical components and conditions requires knowledge of the assay mode, microplate, fluid level, total fluid volume, and sensed volume, among other parameters. Optical components may be changeable manually or automatically, depending on the component. For example, the size of the sensed volume may be adjusted manually by replacing the fiber optic cables adjacent the examination area, and manually or automatically by changing the apertures in front of the fiber optic cables. Similarly, the position of the sensed volume may adjusted manually, or automatically by scanning a positive control well or wells to obtain the maximum signal given the average fluid level in the wells. Manually changeable components may include standard or "quick-change" components.

Calibration of the analyzer may include using a calibration plate. A calibration plate may be shaped like a microplate and include features that can be manually, optically, mechanically, and/or electronically recognized. For example, a calibration plate may include precisely located apertures, mirrors, light sources (such as light-emitting diodes (LEDs)), and/or fluorescent reference standards to verify that the optics, detection, and positioning systems are operating properly.

Reading by the analyzer may be performed in five phases. Phase 1 comprises loading a microplate in the transporter. During this phase, a person, robot, or microplate feeder mechanism places the microplate on the microplate transporter of the X,Y stage. A computer-controlled X,Y microplate registration mechanism ensures that microplates have the correct alignment relative to the optics beam.

Phase 2 comprises sensing the microplate in the transporter. During this phase, a sensor is activated that tells the local or system controller that the microplate has been delivered. The local controller can begin reading the microplate either after sensing the microplate or after receiving a command from the system controller to start reading.

Phase 3 comprises finding the top of the microplate. During this phase, the top of the microplate is found with the top-of-the-plate sensor located in the optics head, followed by computer-controlled adjustment of the Z-position of the optics head.

Phase 4 comprises reading the microplate. During this phase, the microplate is moved automatically from well to well to allow analysis of the contents of each well by use of a high performance motion control system with preselected acceleration/deceleration profiles and settling times to provide maximum possible throughput with minimum acceptable read error.

Phase 5 comprises unloading the microplate from the transporter.

Assay Modes

The analyzer may support a variety of assay modes, including (1) luminescence intensity, (2) luminescence polarization, (3) time-resolved luminescence, (4) chemiluminescence, and (5) absorbance. Aspect of these assay modes are described below to show the versatility and sensitivity of the analyzer. Additional assays and/or alternative methods for performing the described assays also may be employed in conjunction with the analyzer provided by the invention. Additional information regarding these assay modes may be found in U.S. Provisional Patent Application Serial No. 60/082,253, filed April 17, 1998, and incorporated herein by reference.

Luminescence Intensity Mode. Luminescence intensity measurements use a continuous light source. Light produced by the light source is routed through a luminophore-specific excitation filter and a low-luminescence fiber optic cable to the optics head. A beamsplitter splits the light, reflecting light into the assay well and transmitting light into a light

monitor. The light monitor checks the light source continuously and can be programmed to alert the user if the light source fails. Light emitted from the assay well may pass back through the beamsplitter and then is routed through a fiber optic cable to an emission filter that conditions the light before detection by a photomultiplier tube.

The analyzer may use confocal optics elements to direct excitation light into the assay well and to detect light emitted from the well, all from a sensed volume that may be small compared to the overall volume of the well. Because the sensed volume does not change with the volume of the assay well, performance in different microplates is virtually identical. Z-position within the well may be set manually or automatically. For homogeneous assays, the location with the highest signal-to-noise (S/N) ratio and highest signal-to-background (S/B) ratio typically is in the middle of the well. For cell-based assays, the location with the highest S/N and S/B ratio typically is at the bottom of the well, where luminescence from the cells is maximized and luminescence from the fluid is minimized. Conditions that optimize the S/N and S/B ratios may be determined empirically.

Luminescence intensity measurements may be made from either the top or bottom of the sample well. Bottom reading delivers a higher signal than top reading because the bottom focal area is larger, but bottom reading also delivers a lower S/N ratio because microplates or other sample containers typically autoluminesce.

The user has full control of analyzer settings through software. For luminescence measurements, the user selects the excitation and emission filters, top or bottom reading, and read time. Optional parameters include the magnitude and duration of plate shaking, well-to-well settle time, and Z-height adjustments.

Luminescence Polarization Mode. Luminescence polarization measurements use the same optical configuration as luminescence intensity measurements, except that polarization measurements always employ emission

and excitation polarization filters and the top optics head. Light from a continuous light source, preferably a xenon-arc source, is routed through an excitation filter, low-luminescence fiber optic cable, and a polarization filter, which typically is in the S orientation. A beamsplitter then splits the light, reflecting polarized light into the assay well and transmitting light into the light monitor. Light emitted from the assay well may pass back through the beamsplitter and then is routed through a fiber optic cable to an emission and polarization filter (in either the S or P orientation) that conditions the light before detection by a photomultiplier tube.

The analyzer makes two measurements for each assay well, one with excitation and emission polarizers aligned and one with excitation and emission polarizers crossed (as described above). Either polarizer may be static or dynamic, and either polarizer may be set to be S or P.

The continuous light source preferably comprises a high-intensity, high-color temperature light source, such as a xenon arc lamp. Such a lamp minimizes photon noise and hence reduces reading time at a given noise level. When combined with the optimized chemiluminescence detection system, the continuous high-intensity light source increases light throughput and decreases background.

As in luminescence intensity mode, confocal optics elements may direct the excitation light into a small sensed volume in a selected region of the well. The best S/N ratio typically is obtained from the middle of each well, because spurious polarization signals from luminophores bound to the well surfaces is minimized. Conditions that optimize the S/N and S/B ratios may be determined empirically.

For luminescence polarization measurements, the user selects the excitation and emission filters, and read time. Optional parameters include the magnitude and duration of plate shaking, well-to-well move time, and Z-height adjustments.

Time-Resolved Luminescence Mode. Time-resolved luminescence measurements use substantially the same optical configuration as luminescence intensity and luminescence polarization measurements, except that time-resolved luminescence methods use the upper optics head and the substitution of a flash lamp, preferably a xenon flash lamp, for a continuous lamp as the light source. The flash lamp creates a brief flash of excitation light, which is followed by time-dependent luminescence. Time-dependent measurements may be delayed to avoid short-lifetime autoluminescence, and hastened to avoid long-lifetime autoluminescence, if desired.

As in luminescence intensity mode, confocal optics elements may direct the excitation light into a small sensed volume in a selected region of the well. The location of the sensed volume can be changed using the Z-height parameter. The optimal S/N and S/B can best be determined empirically.

For time-resolved luminescence, the user selects the excitation and emission filters, delay time, integration time, and cycle time: Optional parameters include the magnitude and duration of plate shaking, well-to-well settle time, and Z-height adjustments.

Chemiluminescence Mode. Chemiluminescence measurements use a dedicated read head and photomultiplier tube adjacent the top optics head and separate from those used in photoluminescence measurements. Light emitted from an assay well is collected through a specially-baffled read head and aperture that reduce well-to-well cross-talk. Collected light then is routed through a low-luminescence fiber optic cable to an optimized photomultiplier tube having relatively low dark counts and a blue-green shifted response.

Alternatively, chemiluminescence measurements may use the photoluminescence optical system, especially if it is desirable to sense chemiluminescence from a sensed volume within the sample container. To reduce background in this mode, the light source module in the photoluminescence system may be "parked" between detectors, so that the associated floating head assembly abuts only a solid surface.

For luminescence measurements, the user can select read time. Optional features include plate shaking, well-to-well settle time, and Z-height adjustments.

Absorbance Mode. Absorbance measurements require a combination of top illumination and bottom detection, or bottom illumination and top detection, and may use continuous or flash light sources.

Measurement Modes

The analyzer may support a variety of measurement modes for detecting luminescence, including (1) photon counting, (2) current integration, and (3) imaging modes. Aspect of these measurement modes are described below to show the versatility and sensitivity of the analyzer. Additional measurement modes and/or alternative methods for performing the described measurement modes also may be employed in conjunction with the analyzer provided by the invention.

Photon-Counting Mode. Transmitted light may be detected in photon-counting mode. In this approach, the photons comprising the detected light are counted, and intensity is reported as the number of counted photons per unit time. Photon counting is well-suited for assays with low light levels, because each photon is individually reported. Conversely, photon counting is ill-suited for assays with high light levels, because the detector may become saturated and unable to distinguish the arrival of one photon from the arrival of more than one photon. Suitable detectors for practicing this method include PMTs.

Current-Integration Mode. Transmitted light also may be detected in current-integration mode. To decrease the average read time per well, the electronics can be configured to integrate the detector current resulting from the luminescence signal until a preset threshold is achieved. This is equivalent to collecting light from the well until a predetermined number of photons are collected. The component of the signal-to-noise ratio due to the photon noise of the emission light then will be equal to the square root of the number of

photons collected by the detector. This feature is implemented using an integrating current-to-voltage converter at the detector output coupled to an analog comparator in parallel with an analog-to-digital converter. At the beginning of each measurement cycle, the integrator is reset and the time required for the integrated detector current to trip the comparator is measured. The integration time is a representation of the number of photons collected and hence the signal level. If the signal is too small to cause the comparator to be tripped within the maximum time allowed for the integration, the analog-to-digital converter is used to digitize the voltage appearing at the output of the integrator. Because the value of the integration capacitor and the voltage across it both are known, the number of photons collected can be calculated by taking the product of the integration capacitance and the measured voltage and dividing it by the electronic charge (1.602×10^{-19} Coulombs per electron). Suitable detectors for practicing this method include PMTs.

Imaging Mode. In addition to analysis of single wells, this invention also supports simultaneous reading of many wells located in a fixed area of a microplate. Large-area fiber optic bundles and an imaging charged-coupled device (CCD) detector make it possible to excite and detect a fixed area of the microplate at once. Using this method, the detection limit and time to read a microplate is constant regardless of the number of wells on the microplate as long as the fiber size in the bundle is small compared to the smallest well to be measured (e.g., > 4 fibers per well) and the CCD pixel size is small compared to the fiber size (e.g., > 4 pixels per fiber). If the fiber optic bundle is randomly oriented, a calculation procedure can be used during setup to map each CCD pixel to a specific location on the microplate. For example, a single microplate well containing a fluorescent compound can be used to map the CCD pixels through the fiber bundle to the microplate surface by repositioning the well repeatedly to include all CCD pixels.

The above description elaborates on the general architecture of the invention, while also describing preferred embodiments. Other related embodiments are possible and may be desirable for specific applications. For

example, it may be desirable to commercialize only a portion of the preferred embodiment to meet the needs of different customers or specific markets. Also, the preferred embodiments provide for an expandable architecture wherein the light sources and detectors can be added as required to provide new assay modalities, or to take advantage of new types of light source and detectors, as they become commercially available. For example, blue LEDs have become commercially available only in the last few years, and blue laser diodes are expected to become commercially available within the next few years. The architecture of the invention is designed to be flexible so as to allow incorporation of newly commercialized technology with the goal of making such technology available to high-throughput screening laboratories at the earliest possible date.

Another alternative embodiment may include a plurality of confocal detection systems mounted in a linear array or matrix. A linear array of 8 or 12 confocal detectors may be used with one or more light sources and 8 or 12 detectors to simultaneously detect an entire row or column of a 96 well microplate. The same detectors could also be used to read 384 or 1536 well plates with the proper aperture installed since the well-to-well pitch of the hedger density plates are evenly divisible into that of the 96 well plate. In another example, the confocal detection systems could be mounted in an n-by-m array and could also detect one or more plate formats.

Accordingly, while the invention has been disclosed in its preferred form, the specific embodiment thereof as disclosed and illustrated herein is not to be considered in a limiting sense, because numerous variations are possible and no single feature, function, or property of the preferred embodiment is essential. The invention is to be defined only by the scope of the issued claims.

WE CLAIM:

1. An apparatus for detecting light from a composition, the apparatus comprising:

a stage for supporting a composition at an examination site;

at least two light sources and a first optical relay structure that directs light from one of the light sources toward the composition;

a detector and a second optical relay structure that directs light from the composition toward the detector; and

a first switch mechanism that alters alignment of the first optical relay structure from one of the light sources to another of the light sources, so that different light sources can be selected and directed toward the examination site for different applications.

2. The apparatus of claim 1, further comprising a second detector and a second switch mechanism that alters alignment of the second optical relay structure from one of the detectors to another of the detectors, so that different detectors can be selected for different applications.

3. The apparatus of claim 1, further comprising at least a third light source, the first switch mechanism being capable of aligning any one of the light sources with the second optical relay structure, so that light from said one of the light sources is directed toward the composition.

4. The apparatus of claim 1, wherein one of the light sources is a high-intensity, high-color temperature arc lamp.

5. The apparatus of claim 1, further comprising a controller that can be preprogrammed to activate the first switch mechanism, so that a selected light source is directed toward the composition for a particular assay.

6. The apparatus of claim 5, further comprising a bar code reader connected to the controller and positioned to read a bar code on a microplate that holds the composition, wherein the bar code contains light source-selection information that is utilized by the controller to activate the first switch mechanism.

7. The apparatus of claim 1, further comprising a filter alignment mechanism holding plural filters positioned near at least two of the light sources, so that any one of the filters can be aligned alternately with any one of the said light sources and the first optical relay structure.

8. The apparatus of claim 7, wherein the filter alignment mechanism includes a filter wheel, and wherein any one of the filters can be aligned with the said light sources and the first optical relay structure by rotating the filter wheel.

9. The apparatus of claim 7, wherein the filter alignment mechanism includes a linear filter holder, and wherein any one of the filters can be aligned with the said light sources and the first optical relay structure by sliding the sliding filter holder.

10. The apparatus of claim 1, wherein the switch mechanism includes a shuttle that transports an end of the first optical relay structure from alignment with one light source into alignment with another light source.

11. The apparatus of claim 1, wherein the first optical relay structure defines a first optical path directed toward the top side of the examination site and a second optical path directed toward the bottom side of the examination site, the first switch mechanism being capable of aligning any one of the light sources with any one of the optical light paths in the second optical relay structure.

12. The apparatus of claim 11, wherein the second optical relay structure defines a third optical path directed toward the top side of the examination site and a fourth optical path directed toward the bottom side of the examination site, further comprising a second switch mechanism that is capable of aligning the detector and any one of the third and fourth optical paths, so that coordinated actuation of the first and second switch mechanisms permits interchangeable configuration of any one of the following light transmission routes to and from a composition located at the examination site: (a) top-illumination and top-detection, (b) top-illumination and bottom-detection, (c) bottom-illumination and top-detection, and (d) bottom-illumination and bottom-detection.

13. The apparatus of claim 1, further comprising an automated registration device that automatically brings successive compositions and the examination site into register for successive analysis of the compositions.

14. The apparatus of claim 1, wherein the stage is configured to hold a microplate having an array of sample wells.

15. An apparatus for detecting light from a composition, the apparatus comprising:

a stage for supporting a composition at an examination site;

a light source and a first optical relay structure that directs light from the light source toward the composition;

at least two detectors and a second optical relay structure that directs light from the composition to one of the detectors; and

a first switch mechanism that alters alignment of the second optical relay structure from one of the detectors to another of the detectors, so that different detectors can be selected for different applications.

16. The apparatus of claim 15, further comprising at least a third detector, the first switch mechanism being capable of aligning any one of the detectors with the second optical relay structure, so that light from the composition is directed to said one of the detectors.

17. The apparatus of claim 15, further comprising a separate detector and a third optical relay structure that directs light from the composition to the separate detector, wherein the first optical relay structure cannot direct light toward the composition when the third optical relay structure directs light from the composition toward the separate detector.

18. The apparatus of claim 17, wherein the separate detector and the third optical relay structure are configured to detect chemiluminescence.

19. The apparatus of claim 15, wherein at least one of the detectors detects photoluminescence.

20. The apparatus of claim 15, wherein at least two of the detectors are photomultiplier tubes or photodiodes, and wherein each photomultiplier tube or photodiode is selected for a different application.

21. The apparatus of claim 15, further comprising a controller that can be preprogrammed to activate the first switch mechanism, so that light transmitted from the composition is directed toward one of the detectors that is selected for a particular assay.

22. The apparatus of claim 21, further comprising a bar code reader connected to the controller and positioned to read a bar code on a microplate that holds the composition, wherein the bar code contains detector-selection information that is utilized by the controller to activate the first switch mechanism.

23. The apparatus of claim 15, further comprising a filter alignment mechanism holding plural filters positioned near at least two of the detectors, so that any one of the filters can be rotated into alignment with any one of the said detectors and the second optical relay structure.

24. The apparatus of claim 23, wherein the filter alignment mechanism includes a filter wheel, and wherein any one of the filters can be aligned with any one of the said detectors and the second optical relay structure by rotating the filter wheel.

25. The apparatus of claim 23, wherein the filter alignment mechanism includes a linear filter holder, and wherein any one of the filters can be aligned with any one of the said detectors and the second optical relay structure by sliding the linear filter holder.

26. The apparatus of claim 15, wherein the first switch mechanism includes a shuttle that transports an end of the second optical relay structure from alignment with one detector into alignment with another detector.

27. The apparatus of claim 15, wherein the second optical relay structure defines a first optical path directed toward the top side of the examination site and a second optical path directed toward the bottom side of the examination site, the first switch mechanism being capable of aligning any one of the detectors with any one of the optical light paths in the second optical relay structure.

28. The apparatus of claim 15, further comprising an automated registration device that automatically brings successive compositions and the examination site into register for successive analysis of the compositions.

29. The apparatus of claim 15, wherein the stage is configured to hold a microplate having an array of sample wells.

30. An apparatus for detecting light from a composition, the apparatus comprising:

a stage for supporting a composition at an examination site, the examination site having a top side and a bottom side;

at least one light source and a first optical relay structure defining a first optical path directed toward the top side of the examination site and a second optical path directed toward the bottom side of the examination site;

at least one detector and a second optical relay structure that directs light from the composition toward the detector; and

a first switch mechanism that alters alignment of the light source from one of the optical paths to the other optical path.

31. The apparatus of claim 30, wherein the second optical relay structure defines a third optical path directed toward the top side of the examination site and a fourth optical path directed toward the bottom side of the examination site, further comprising a second switch mechanism that is capable of aligning the detector and any one of the third and fourth optical paths, so that coordinated actuation of the first and second switches mechanisms permits interchangeable configuration of any one of the following light transmission routes to and from a composition located at the examination site: (a) top-illumination and top-detection, (b) top-illumination and bottom-detection, (c) bottom-illumination and top-detection, and (d) bottom-illumination and bottom-detection.

32. The apparatus of claim 31, further comprising a first optics head positioned above the stage, and a second optics head positioned below the stage, wherein the first and third optical paths are directed through the first optics head, and the second and fourth optical paths are directed through the second optics head.

33. The apparatus of claim 30, further comprising at least a second light source, wherein the first switch mechanism is capable of aligning any one of the optical paths with any one of the light sources.

34. The apparatus of claim 30, further comprising at least a second detector and a second switch mechanism that alters alignment of the second optical relay structure from one of the detectors to another of the detectors, so that different detectors can be selected for different applications.

35. The apparatus of claim 30, further comprising at least a second light source, the first switch mechanism being capable of aligning any one of the light sources with the first optical relay structure, so that light from said one of the light sources is directed toward the composition.

36. The apparatus of claim 35, further comprising a filter alignment mechanism holding plural filters positioned near the two light sources, so that any one of the filters can be aligned with any one of the light sources and the first optical relay structure.

37. The apparatus of claim 35, wherein one of the light sources is a high-intensity, high-color temperature arc lamp.

38. The apparatus of claim 30, further comprising a controller that can be preprogrammed to activate the first switch mechanism, so that light from the light source is directed through one of the optical paths that is selected as being the most appropriate for a particular assay.

39. The apparatus of claim 38, further comprising a bar code reader connected to the controller and positioned to read a bar code on a microplate that holds the composition, wherein the bar code contains information that is utilized by the controller to activate the first switch mechanism.

40. The apparatus of claim 30, wherein the first switch mechanism includes a shuttle that transports an end of one of the optical paths into alignment with the light source.

41. An apparatus for detecting light from a composition, the apparatus comprising:

a stage for supporting a composition at an examination site having a top side and a bottom side;

at least one light source and a first optical relay structure that directs light from the light source toward the composition;

at least one detector and a second optical relay structure defining a first optical path directed toward the top side of the examination site and a second optical path directed toward the bottom side of the examination site; and

a first switch mechanism that alters alignment of the detector from one of the optical paths to the other optical path.

42. The apparatus of claim 41, further comprising at least a second detector, wherein the first switch mechanism is capable of aligning any one of the optical paths with any one of the detectors.

43. The apparatus of claim 41, further comprising at least a second light source and a second switch mechanism that alters alignment of the first optical relay structure from one of the light sources to another of the light sources, so that different light sources can be selected for different applications.

44. The apparatus of claim 41, further comprising at least a second detector, the first switch mechanism being capable of aligning any one of the detectors with the second optical relay structure, so that light from said one of the detectors is directed toward the composition.

45. The apparatus of claim 44, further comprising a filter alignment mechanism holding plural filters positioned near the two detectors, so that any one of the filters can be aligned with any one of the detectors and the second optical relay structure.

46. The apparatus of claim 41, further comprising a controller that can be preprogrammed to activate the first switch mechanism, so that light transmitted from the composition is directed through one of the optical paths that is selected as being the most appropriate for a particular assay.

47. The apparatus of claim 46, further comprising a bar code reader connected to the controller and positioned to read a bar code on a microplate that holds the composition, wherein the bar code contains information that is utilized by the controller to activate the first switch mechanism.

48. The apparatus of claim 41, wherein the first switch mechanism includes a shuttle that transports an end of one of the optical paths into alignment with the light source.

49. A light switching module for a light detection apparatus, the light switching module comprising:

at least two light fixture slots, each slot having a light transmission port; and

a shuttle having at least one light transmission conduit, the shuttle being moveable relative to the slots, so that any one of the light transmission ports can be aligned with the light transmission conduit, wherein the conduit has a distal end that can be positioned near an examination site for conveying light between the examination site and a selected light fixture in one of the slots.

50. The light switching module of claim 49, wherein the light fixture slots are configured to hold light sources.

51. The light switching module of claim 49, wherein the light fixture slots are configured to hold detectors.

52. The light switching module of claim 49, further comprising third and fourth light fixture slots, each of said third and fourth light fixture slots having a light transmission port that can be aligned with the light transmission conduit.

53. The light switching module of claim 49, further comprising a filter alignment mechanism holding a plurality of filters, so that any one of the filters can be aligned with any one of the light transmission ports.

54. A method of detecting light from a sample, the method comprising:

providing a plurality of light sources, at least one detector, and an optical relay structure in a light detection instrument, wherein the optical relay structure directs light from one of the light sources toward a composition at an examination site;

selecting one of the light sources using a first switch mechanism that alters alignment of the optical relay structure from one of the light sources to another of the light sources;

relaying light from the selected light source through the optical relay structure to the composition; and

detecting light transmitted from the composition.

55. The method of claim 54, further comprising:

providing at least a second detector; and

selecting one of the detectors to receive light transmitted from the composition.

56. The method of claim 54, further comprising:

providing a first optical path that directs light toward the top of the composition, and a second optical path that directs light toward the bottom of the composition; and

selecting one of the optical paths to transmit light from the light source to the composition.

57. A method of detecting light from a sample, comprising:

providing at least one light source, a plurality of detectors, and an optical relay structure in a light detection instrument, wherein the optical relay structure directs light from a composition at an examination site toward one of the detectors;

selecting one of the detectors using a first switch mechanism that alters alignment of the first optical relay structure from one of the detectors to another of the detectors;

illuminating the composition; and

relaying light from the composition through the optical relay structure to the selected detector.

58. The method of claim 57, further comprising:

providing a first optical path that receives and directs light from the top of the composition, and a second optical path that receives and directs light from the bottom of the composition; and

selecting one of the optical paths to transmit light from the composition to the one of the detectors.

59. An apparatus for detecting light transmitted from a composition, the apparatus comprising:

a stage for supporting a composition at an examination site,

a plurality of adjacent light source compartments, each compartment having an opening for transmitting light from a light source contained in the compartment,

a detector compartment, the compartment having an opening for transmitting light to a detector contained in the compartment, and

a light source selection device including a first light-transmission pathway for directing light from a first light source in a first light source compartment toward a composition at the examination site when the light source selection device is set in a first position, and a second light-transmission pathway for directing light from a second light source in a second light source compartment toward the composition when the light source selection device is set in a second position, so that different light sources can be used for different applications by actuating the light source selection device between the first and second positions.

60. The apparatus of claim 59, further comprising

at least one optical head having an input port that receives light from one of the light sources, and an output port that directs light, transmitted through the input port, directly to the examination site, so that when the light source selection device is in the first position, the first light-transmission pathway transmits light from the first light source to the input port of the optical head, and when the light source selection device is in the second position, the second light-transmission pathway transmits light from the second light source to the input port of the optical head.

61. An apparatus for detecting light transmitted from a composition, the apparatus comprising:

a stage for supporting a composition at an examination site,

a light source compartment, the compartment having an opening for transmitting light from a light source contained in the compartment,

a plurality of adjacent detector compartments, each compartment having an opening for transmitting light to a detector contained in the compartment, and

a detector selection device including a first light-transmission pathway for directing light transmitted from a composition at the examination site toward a first detector when the detector selection device is set in a first position, and a second light-transmission pathway for directing light from the composition toward a second detector when the detector selection device is set in a second position, so that different detectors can be used for different applications by actuating the detector selection device between the first and second positions.

62. The apparatus of claim 61, further comprising at least one optical head having an input port that receives light directly from the examination site, and an output port that transmits light toward the detectors, so that when the detector selection devices is in the first position, the first light-transmission pathway transmits light from the output port of the optical head to the first detector, and when the detector selection device is in the second position, the second light-transmission pathway transmits light from the output port of the optical head to the second detector.

63. An apparatus for detecting light transmitted from a composition, the apparatus comprising:

a stage for supporting a composition in an examination site, the composition being contained in a spatial volume lying between boundary interfaces located at different points along a Z-axis, wherein the Z-axis is substantially perpendicular to the stage;

an automated registration device that automatically brings successive compositions and the examination site into register for successive analysis of the compositions;

a light source positioned to deliver light to the composition in the examination site;

a detector positioned to receive light transmitted from the composition in the examination site; and

an optical relay structure located between the light source and the detector, the optical relay structure being capable of transmitting light substantially exclusively from a sensed volume of the composition, wherein the sensed volume is spaced substantially away from at least one of the boundary interfaces of the composition.

64. The apparatus of claim 63, further comprising a Z-axis adjustment device that automatically adjusts the relative positions of the sensed volume and the composition along the Z-axis.

65. The apparatus of claim 64, wherein the optical relay structure includes confocal optics elements substantially contained within an optics head positioned above or below the stage, the Z-axis adjustment device including a drive mechanism that moves the optics head relative to the Z-axis.

66. The apparatus of claim 63, wherein X, Y-axes are defined perpendicular to each other, perpendicular to the Z-axis and parallel to the stage, further comprising an X, Y-axes adjustment device that automatically adjusts the relative positions of the sensed volume and the composition along the X and Y axes.

67. The apparatus of claim 66, wherein the X, Y-axes adjustment device can be programmed to convey successive compositions to the examination site.

68. The apparatus of claim 67, wherein the successive compositions are contained in wells of a microplate.

69. The apparatus of claim 63, wherein the sensed volume is spaced substantially away from all the boundary interfaces.

70. The apparatus of claim 63, wherein the sensed volume has a waist region in a sample plane, and a Z-pick-up, the diameter of the waist region being approximately half the dimension of the Z-pick-up.

71. The apparatus of claim 63, wherein the optical relay structure includes an aperture substantially centered about the Z-axis and contained in an image plane conjugate to a sample plane intersecting the sensed volume.

72. The apparatus of claim 63, wherein the apparatus is capable of detecting light in at least two of the following types of assays: luminescence intensity, photoluminescence polarization, chemiluminescence, photoluminescence lifetime absorbance, luminescence resonance energy transfer, and luminescence imaging.

73. The apparatus of claim 63, wherein the detector detects light of longer wavelength than the light delivered to the composition from the light source.

74. The apparatus of claim 63, further comprising an automated registration device controller for preprogramming the relative movement into registration of successive compositions and the examination site.

75. The apparatus of claim 63, wherein the light source is a lamp, or a light-emitting diode, or a laser, or a flash lamp, or a particle accelerator.

76. The apparatus of claim 63, wherein the light source is one of a plurality of light sources positioned at a source station, and further comprising a switching mechanism for interchangeably connecting different light sources to the optical relay structure for different applications.

77. The apparatus of claim 76, wherein the switching mechanism includes a shuttle having one side connected to a fiber optic element leading toward the stage, and a second side substantially facing the light sources, the shuttle being movable relative to the light sources, so that different light sources can be selectively transmitted through the fiber optic element to a composition at the examination site.

78. The apparatus of claim 76, further comprising a filter wheel connected to the source station, the filter wheel containing a plurality of filters and being rotatable about a rotational axis so that a given filter can be interchangeably interposed between different light sources and the optical relay structure.

79. The apparatus of claim 63, wherein the detector is a photomultiplier tube, or a photodiode, or a charge-coupled device.

80. The apparatus of claim 63, wherein successive compositions are held in adjacent wells in a microplate.

81. The apparatus of claim 80, wherein the number of wells in the microplate is 96, or 384, or 1536.

82. The apparatus of claim 63, wherein the optical relay structure simultaneously transmits light to the detector from compositions contained in a plurality of microplate wells.

83. The apparatus of claim 63, wherein the optical relay structure delivers light from the light source at an angle relative to the Z-axis exceeding the critical angle for establishing an evanescent field in the composition.

84. The apparatus of claim 63, wherein the optical relay structure delivers light from the light source at an angle relative to the Z-axis below the critical angle for establishing an evanescent field in the composition.

85. The apparatus of claim 63, wherein the sensed volume is diffraction limited.

86. The apparatus of claim 63, wherein the light source produces high-intensity, high-color temperature light.

87. The apparatus of claim 86, wherein the light source is a xenon arc lamp.

88. The apparatus of claim 63, wherein the automated registration device includes a transporter having a mechanism that releasably grips and moves a sample container to and from the examination site.

89. The apparatus of claim 88, wherein the transporter is dimensioned to grip and carry a microplate.

90. The apparatus of claim 88, wherein the transporter is the stage.

91. The apparatus of claim 90, further comprising

a housing, the transporter being movable along a path running between a loading position and the examination site, the loading position being substantially outside the housing, so that compositions can be easily loaded on and unloaded from the transporter when the transporter is in the loading position, and the transporter can deliver compositions to and from the examination site inside the housing before and after analysis.

92. The apparatus of claim 91, further comprising

a stacking unit mounted next to the loading position outside the housing, the stacking unit being configured to hold a plurality of sample containers, and to feed sample containers to the transporter one at a time.

93. The apparatus of claim 92, wherein the sample containers are microplates.

94. The apparatus of claim 90, wherein the transporter is open in the center so that when the transporter is in the examination site, light can be transmitted from below the stage to a composition in the examination site.

95. The apparatus of claim 63, wherein the optical relay structure includes a first aperture and a first lens positioned along a light path between the light source and the examination site or between the detector and the examination site.

96. The apparatus of claim 95, wherein the optical relay structure includes a second aperture and a second lens, the first aperture and the first lens being positioned along a light path between the light source and the examination site, the second aperture and the second lens being positioned along a light path between the detector and the examination site so that light is transmitted substantially exclusively to and from the same sensed volume in a composition at the examination site.

97. The apparatus of claim 95, wherein the optical relay structure includes at least one fiber optic element, the first aperture being defined by the dimension of an end of the fiber optic element.

98. The apparatus of claim 95, wherein the first aperture is defined in a mask structure at an end of a fiber optic element.

99. The apparatus of claim 95, wherein the optical relay structure includes a second aperture, the first and second apertures having different dimensions, and an aperture switching mechanism for interchangeably positioning a selected aperture in the light path leading to or from a sensed volume in a composition at the examination site, so that the size of the sensed volume can be altered by switching between the first and second apertures.

100. The apparatus of claim 95, wherein the diameter of the first aperture is adjustable.

101. The apparatus of claim 95, wherein the first aperture and the first lens are contained in a first optics head positioned near the stage.

102. The apparatus of claim 101, wherein the first optics head is positioned above the stage.

103. The apparatus of claim 101, wherein the first optics head is positioned below the stage.

104. The apparatus of claim 101, wherein the first optics head has a light entrance port optically connected to the light source, and a light exit port optically connected to the detector, so that illumination and detection of light transmitted from a composition in the examination site can be carried out from the same side of the stage.

105. The apparatus of claim 101, wherein the light entrance port and the light exist port are configured to transmit light in directions that are substantially perpendicular to each other.

106. The apparatus of claim 105, wherein the first optics head includes a planar beam splitter oriented at 45 degree angles to the directions of light transmission.

107. The apparatus of claim 102, wherein the optical relay structure includes a second optics head positioned below the stage, each optics head having a light entrance port optically connected to the light source, and a light exit port optically connected to the detector, and a switch control mechanism capable of interchangeably configuring any one of the following light transmission routes to and from a sensed volume in a composition located at the examination site: (a) top-illumination and top-detection, (b) top-illumination and bottom-detection, (c) bottom-illumination and top-detection, and (d) bottom-illumination and bottom-detection.

108. An apparatus for detecting light transmitted from a composition, the apparatus comprising:

a stage for supporting a composition in a spatial volume having boundary interfaces located along surfaces in a microplate well;

a light source positioned to deliver light from the light source into the composition;

a detector; and

an optical relay structure that is capable of transmitting light substantially exclusively from a sensed volume of the composition to the detector, wherein the sensed volume is spaced substantially away from the boundary interfaces of the composition.

109. The apparatus of claim 108, wherein a Z-axis is defined perpendicular to the stage, further comprising a Z-axis adjustment device that automatically adjusts the relative positions of the sensed volume and the composition along the Z-axis.

110. The apparatus of claim 108, wherein X, Y-axes are defined perpendicular to each other, perpendicular to the Z-axis and parallel to the stage, further comprising an X, Y-axes adjustment device that automatically adjusts the relative positions of the sensed volume and the composition along the X and Y-axes.

111. The apparatus of claim 108, wherein a Z-axis is defined substantially perpendicular to the stage of an examination site, the optical relay structure including an aperture substantially centered about the Z-axis and contained in an image plane conjugate to a sample plane intersecting the sensed volume.

112. The apparatus of claim 108, wherein the apparatus is capable of detecting light in at least two of the following types of assays: luminescence intensity, photoluminescence polarization, chemiluminescence, photoluminescence lifetime absorbance, luminescence resonance energy transfer, luminescence imaging.

113. The apparatus of claim 108, wherein the detector detects light of longer wavelength than the light delivered to the composition from the light source.

114. The apparatus of claim 108, wherein the light source is a lamp, or a light-emitting diode, or a laser, or a flash lamp, or a particle accelerator.

115. The apparatus of claim 108, wherein the detector is a photomultiplier tube, or a photodiode, or a charge-coupled device.

116. The apparatus of claim 108, wherein the microplate well is contained in a microplate, wherein the number of wells in the microplate is 96, or 384, or 1536.

117. The apparatus of claim 108, wherein the microplate well containing the composition is located at an examination site, the optical relay structure including a first aperture and a first lens positioned along a light path between the detector and the examination site.

118. The apparatus of claim 108, wherein the optical relay structure includes a second aperture and a second lens positioned along a light path running between the light source and the examination site.

119. The apparatus of claim 117, wherein the optical relay structure includes at least one fiber optic element, the first aperture being defined by the dimension of an end of the fiber optic element.

120. The apparatus of claim 117, wherein the first aperture is defined in a mask structure at an end of a fiber optic element.

121. The apparatus of claim 117, wherein the optical relay structure includes a second aperture, the first and second apertures having different dimensions, and an aperture switching mechanism for interchangeably positioning a selected aperture in the light path leading to or from a sensed volume in a composition at the examination site, so that the size of the sensed volume can be altered by switching between the first and second apertures.

122. The apparatus of claim 117, wherein the first aperture and the first lens are contained in a first optics head positioned near the stage.

123. The apparatus of claim 122, wherein the first optics head is positioned above the stage.

124. The apparatus of claim 122, wherein the first optics head is positioned below the stage.

125. The apparatus of claim 122, wherein the first optics head has a light entrance port optically connected to the light source, and a light exit port optically connected to the detector, so that illumination and detection of light transmitted from a composition in the examination site can be carried out from the same side of the stage.

126. The apparatus of claim 125, wherein the light entrance port and the light exit port are configured to transmit light in directions that are substantially perpendicular to each other.

127. The apparatus of claim 126, wherein the first optics head includes a planar beamsplitter oriented at 45-degree angles to the directions of light transmission.

128. The apparatus of claim 123, wherein the optical relay structure includes a second optics head positioned below the stage, each optics head having a light entrance port optically connected to the light source, and a light exit port optically connected to the detector, and a switch control mechanism capable of interchangeably configuring any one of the following light transmission routes to and from a sensed volume in a composition located at the examination site: (a) top-illumination and top-detection, (b) top-illumination and bottom-detection, (c) bottom-illumination and top-detection, and (d) bottom-illumination and bottom-detection.

129. An apparatus for detecting light transmitted from a composition, the apparatus comprising:

a stage for supporting a composition in a spatial volume having boundary interfaces located along surfaces in a microplate well;

a light source;

an optical relay structure that is capable of delivering light from the light source substantially exclusively to a sensed volume of the composition, wherein the sensed volume is spaced substantially away from the boundary interfaces of the composition; and

a detector positioned to receive light transmitted from the sensed volume of the composition.

130. An apparatus for detecting photoluminescence emitted by a sample, the apparatus comprising:

a stage configured to hold a microplate having an array of sample wells;

a light source located at one end of a first light path leading toward the stage and configured to deliver light to induce photoluminescence in a sample contained in at least one of the sample wells;

a detector located at one end of a second light path leading toward the stage and configured to detect photoluminescence emitted by the sample; and

a confocal optics element operatively positioned along the first light path or the second light path, and configured substantially to prevent light from focusing outside a pre-selected sensed volume inside the sample, or configured substantially to prevent detection of photoluminescence originating outside the sensed volume.

131. An apparatus for detecting luminescence emitted by a sample, the apparatus comprising:

a stage configured to hold a sample at an examination site for analysis;

an alignment device configured to adjust the relative positions of the stage and the examination site, so that the sample and the examination site can be brought into alignment before detection of luminescence, and removed from alignment after such detection;

an alignment device controller configured automatically to control the alignment device, so that successive samples can be brought into alignment with the examination site for detection of luminescence;

an optical focusing structure configured sequentially to focus luminescence from the portion of the sample positioned in a sample plane into a series of image planes, wherein the image planes include at least one intermediate image plane and one terminal image plane;

a detector configured to detect luminescence emitted by the sample, wherein the detector is positioned substantially in the terminal image plane; and

an emission confocal optics element configured substantially to prevent detection of luminescence originating outside a sensed volume intersecting the sample plane, wherein the emission confocal optics element is positioned between the sample and the detector substantially in an intermediate image plane.

132. The apparatus of claim 131, wherein the optical focusing structure includes at least one lens positioned along a light path leading from the sample plane to the detector.

133. The apparatus of claim 131, wherein the emission confocal optics element defines an aperture.

134. The apparatus of claim 133, wherein the aperture is adjustable.

135. The apparatus of claim 131, further comprising:

a light source configured to deliver light to induce luminescence in the sample; and

an excitation confocal optics element configured substantially to prevent light from the light source from focusing outside the portion of the sample plane contained in the sensed volume;

wherein the excitation confocal optics element is positioned substantially in an intermediate image plane located between the light source and the sample; and

wherein there are at least two intermediate image planes, with the emission confocal optics element and the excitation confocal optics element positioned in different image planes.

136. A method of detecting light transmitted from a composition, the method comprising:

automatically bringing into register a succession of compositions and an examination site for successive analysis of the compositions, wherein each composition is contained between top and bottom boundary interfaces;

transmitting light into compositions at the examination site; and

detecting light substantially exclusively from a sensed volume of the compositions that is spaced substantially away from at least one of the boundary interfaces.

137. A high-throughput method of detecting light transmitted from a succession of samples, the method comprising:

automatically and sequentially aligning a succession of samples at an examination site;

for each sample, focusing light originating from the waist region of a sensed volume into a series of image planes, beginning with at least one intermediate image plane and terminating with a terminal image plane;

positioning a detector in the terminal image plane to detect light transmitted by the sample; and

positioning an emission confocal optics element in an intermediate image plane, wherein the emission confocal optics element is configured substantially to prevent detection of light originating outside the sensed volume.

138. The high-throughput method of claim 137, further comprising:

positioning a light source to induce emission of light by the sample; and

positioning an excitation confocal optics element in an intermediate image plane, wherein the excitation confocal optics element is configured substantially to prevent light from the light source from focusing outside the waist region of the sensed volume.

139. A device for detecting light from a sample, the device comprising:

a stage for supporting a sample at an examination site;

an optics head positioned above or below the examination site;

a first drive mechanism that adjusts the distance between the optics head and the examination site;

a first optical relay structure connected to the optics head for transmitting luminescence from the examination site to a first detector; and

a second optical relay structure connected to the optics head and dedicated to transmitting chemiluminescence from the examination site to a second detector.

140. The device of claim 139, further comprising a second drive mechanism, wherein the first drive mechanism moves the optics head along a Z axis perpendicular to the stage, and the second drive mechanism moves the stage along X and Y axes perpendicular to the Z axis.

141. The device of claim 139, wherein the second detector is a photomultiplier tube or a charge-coupled device.

142. The device of claim 139, wherein the first optical relay structure is capable of transmitting luminescence substantially exclusively from a sensed volume within the sample, and the second optical relay structure is capable of transmitting chemiluminescence from substantially the entire sample.

143. A device for detecting chemiluminescence from a sample, the device comprising:

a stage for supporting a sample in a well at an examination site;

an optical relay structure having an end directed toward the examination site for transmitting chemiluminescence from the sample to a detector;

a drive mechanism that adjusts the distance between the end of the optical relay structure and the examination site; and

a sensor, positioned near the end of the optical relay structure, that detects proximity of the end of the optical relay structure relative to the well.

144. The device of claim 143, wherein the drive mechanism and the sensor are programmed to work cooperatively to sense a height of the well, and then to locate the end of the optical relay structure so that it is spaced a distance G from the well, G being just high enough so that another well can be moved smoothly into alignment with the end of the optical relay structure without altering G.

145. The device of claim 143, wherein the sensor is a mechanical switch, or an optical switch, or an acoustical switch.

146. A device for detecting chemiluminescence from a sample, the device comprising:

a stage for supporting a sample in a well at an examination site;

an optical relay structure having an end directed toward the examination site for transmitting chemiluminescence from the sample to a detector; and

a mask structure having plural apertures of different dimensions, moveably mounted relative to the end of the optical relay structure, so that an effective diameter for the optical relay structure can be selected to complement a particular dimension of the well.

147. The device of claim 146, wherein the well has a diameter, the mask structure having an aperture with a diameter approximately equal to the diameter of the well.

148. The device of claim 146, wherein at least some of the apertures are configured to correspond to wells in microplates having one or more of the following well formats: 96, 384, 1536, 3456, and 9600.

149. A device for detecting chemiluminescence from a sample, the device comprising:

a stage for supporting a sample in a well at an examination site;

an optical relay structure having an end directed toward the examination site for transmitting chemiluminescence from the sample to a detector; and

a baffle surrounding the end of the optical relay structure that blocks extraneous light from outside the well from entering the optical relay structure, wherein the baffle has a substantially black surface with rugosities, generally facing the stage, and configured to absorb light.

150. The device of claim 149, wherein the optical relay structure includes a fiber optic cable having a diameter, the baffle having a diameter at least about twice the diameter of the fiber optic cable.

151. The device of claim 149, wherein the baffle further functions as a mask structure having plural apertures of different dimensions, movably mounted relative to the end of the optical relay structure, so that an effective diameter for the optical relay structure can be selected to complement a particular dimension of the well.

152. A device for detecting chemiluminescence from a sample, the device comprising:

a stage for supporting a sample at an examination site in one of a plurality of microplate wells, the wells having top edges defining an upper plane; and

an optical relay structure having an end directed toward the examination site for transmitting chemiluminescence from the sample to a detector, wherein the end of the optical relay structure is spaced a distance G from the upper plane, G being just high enough so that another well can be moved smoothly into alignment with the end of the optical relay structure without altering G.

153. The device of claim 152, wherein G is approximately in the range of 0.15 to 0.25 mm.

154. The device of claim 152, further comprising a drive mechanism that adjusts the distance between the end of the optical relay structure and the stage.

155. The device of claim 154, further comprising a controller that is preprogrammed to operate the drive mechanism so that a desired G height is set for a specific microplate.

156. The device of claim 152, further comprising a sensor associated with the optical relay structure for detecting the proximity of the end of the optical relay structure relative to the upper plane.

157. A device for detecting light from a sample, the device comprising:

a stage configured to hold a microplate having an array of sample wells; and

a plurality of optical relay structures having ends directed toward the microplate, the optical relay structures disposed so that each optical relay structure transmits light to an associated detector from a different set of sample wells, a different detector being associated with each optical relay structure, so that light can be detected more quickly from the entire microplate.

158. The device of claim 157, wherein the optical relay structures are disposed as an array that complements the array of sample wells in at least a portion of the microplate.

159. A device for transmitting light through an aperture in a surface, the device comprising:

an optical relay structure having an end configured to transmit light; and

an opaque collar positioned around the end and configured to reorient to conform to the surface when the end and the aperture are aligned, so that a substantially light-tight junction is formed.

160. The device of claim 159, wherein the optical relay structure includes a central axis and the opaque collar includes a leading rim edge defining an end plane, the opaque collar reorienting by changing angle relative to the central axis.

161. The device of claim 159, wherein the opaque collar is spring-biased relative to the end, so that the opaque collar is forced against the surface when the end and the aperture are aligned.

162. The device of claim 159, further comprising:

a base;

a spring operatively associated with the base, wherein the opaque collar is spring-biased relative to the end when the spring is compressed between the opaque collar and the base; and

a stop mechanism configured to limit relative movement of the opaque collar and the base.

163. The device of claim 159, wherein the optical relay structure includes a fiber optic cable, a light source, or a detector.

164. The device of claim 159, wherein the surface is substantially flat.

165. The device of claim 159, further comprising a registration mechanism configured to align the end and the aperture.

166. The device of claim 165, wherein the surface includes two apertures, and the registration mechanism is capable of aligning the end with either aperture.

167. The device of claim 165, wherein the registration mechanism is capable of aligning the end with a portion of the surface not including an aperture to prevent the optical relay structure from transmitting light.

168. The device of claim 159, wherein at least a portion of the opaque collar deforms under pressure from the spring substantially to conform to asperities in the surface.

169. The device of claim 159, further comprising a light source positioned on a side of the surface opposite the optical relay structure, so that when the end of the optical relay structure is aligned with the aperture, light from the light source can be transmitted through the aperture and optical relay structure substantially without leakage.

170. The device of claim 159, further comprising a detector positioned on a side of the surface opposite the optical relay structure, so that when the end of the optical relay structure is aligned with the aperture, light can be transmitted through the optical relay structure and aperture to the detector substantially without leakage.

171. A device for transmitting light through an aperture in a surface, the device comprising:

an optical relay structure having an end configured to transmit light; and

an opaque collar positioned around the end and spring-biased relative to the end, so that the opaque collar is forced against the surface when the end and the aperture are aligned, so that a substantially light-tight junction is formed.

172. The device of claim 171, wherein the opaque collar is configured to reorient to conform to the surface when the end and the aperture are aligned.

173. The device of claim 171, further comprising:

a base;

a spring operatively associated with the base, wherein the opaque collar is spring-biased relative to the end when the spring is compressed between the opaque collar and the base; and

a stop mechanism configured to limit relative movement of the opaque collar and the base.

174. The device of claim 171, wherein the optical relay structure includes a fiber optic cable, a light source, or a detector.

175. The device of claim 171, wherein the surface is substantially flat.

176. The device of claim 171, further comprising a registration mechanism configured to align the end and the aperture.

177. The device of claim 176, wherein the surface includes two apertures, and the registration mechanism is capable of aligning the end with either aperture.

178. The device of claim 176, wherein the registration mechanism is capable of aligning the end with a portion of the surface not including an aperture to prevent the optical relay structure from transmitting light.

179. The device of claim 171, wherein at least a portion of the opaque collar deforms under pressure from the spring substantially to conform to asperities in the surface.

180. The device of claim 171, further comprising a light source positioned on a side of the surface opposite the optical relay structure, so that when the end of the optical relay structure is aligned with the aperture, light from the light source can be transmitted through the aperture and optical relay structure substantially without leakage.

181. The device of claim 171, further comprising a detector positioned on a side of the surface opposite the optical relay structure, so that when the end of the optical relay structure is aligned with the aperture, light can be transmitted through the optical relay structure and aperture to the detector substantially without leakage.

182. A device for transmitting light through an aperture in a surface, the device comprising:

an optical relay structure having a central axis and an end configured to transmit light;

first and second opaque walls positioned around the end, the opaque walls being concentric and partially overlapping; and

a biasing mechanism to force the opaque walls in opposite directions parallel to the central axis, so that the first opaque wall is spring-biased against the surface to form a substantially light-tight junction when the end and the aperture are aligned.

183. The device of claim 182, wherein one of the opaque walls has a flange that limits relative movement of the walls.

184. A method of light-tight switching between two light fixtures, the method comprising:

providing first and second light fixtures housed in first and second light fixture slots, each light fixture slot having an aperture for transmitting light, wherein the apertures are located on a common surface;

providing a device for transmitting light through the aperture, the device including (1) an optical relay structure having an end configured to transmit light, and (2) an opaque collar positioned around the end;

aligning the device with one of the apertures;

forming a substantially light-tight junction by reorienting the opaque collar to conform to the surface; and

aligning the device with the other of the apertures by translating the device so that the opaque collar maintains substantially light-tight contact with the common surface.

185. The method of claim 184, wherein the two light fixtures are light sources.

186. The method of claim 184, wherein the two light fixtures are detectors.

187. A method of light-tight switching between two light fixtures, the method comprising:

providing first and second light fixtures housed in first and second light fixture slots, each light fixture slot having an aperture for transmitting light, wherein the apertures are located on a common surface;

providing a device for transmitting light through the aperture, the device including (1) an optical relay structure having an end configured to transmit light and (2) an opaque collar positioned around the end;

aligning the device with one of the apertures;

forming a substantially light-tight junction by spring-biasing the opaque collar relative to the end, so that the opaque collar is forced against the surface; and

aligning the device with the other of the apertures by translating the device so that the opaque collar maintains substantially light-tight contact with the common surface.

188. A device for holding an optical filter, the device comprising:

a filter barrel having an inner wall and a stop structure;

a removable annular friction member inside the filter barrel; and

at least one optical filter sandwiched between the stop structure and the friction member, wherein the friction member is held in place relative to the inner wall by static friction, without any thread, groove, or adhesive.

189. The device of claim 188, wherein the inner wall is substantially parallel to the optical filter.

190. The device of claim 188, wherein the inner wall has a funnel portion that graduates in diameter in a direction progressing away from the stop structure.

191. The device of claim 188, wherein the friction member is a compressible ring having an uncompressed outer diameter greater than the inner diameter of the inner wall.

192. The device of claim 191, wherein the compressible ring exerts a force on the inner wall that provides sufficient static friction to hold the optical filter snugly in place during routine use, while also permitting easy removal when replacing optical filters.

193. The device of claim 188, wherein the optical filter is an intensity filter, a spectral filter, or a polarization filter.

194. A tool device for loading an optical filter into a holder, the device comprising a funnel structure having a top end and a lower edge configured to rest on top of a filter holder, wherein the funnel structure has an inner diameter that enlarges gradually in a direction from the lower edge toward the top end.

195. The device of claim 194, further comprising a slug for applying pressure to a friction member when loading the optical filter, wherein the slug and the optical filter have approximately equivalent peripheral dimensions.

196. An optical filter holder system, the system comprising:

a holder having a plurality of apertures; and

first and second sets of filter cartridges configured to fit in the apertures, each of the first set of filter cartridges having an optical filter permanently fixed in the filter cartridge, each of the second set of filter cartridges having a mechanism that permits easy replacement of different optical filters in the same filter cartridge.

197. The system of claim 196, wherein the holder includes a filter wheel.

198. The system of claim 196, wherein each of filter cartridges has a lower portion that is threaded to screw into any one of the apertures.

199. The system of claim 196, wherein the mechanism comprises:

a filter barrel having an inner wall and a stop structure; and

a removable annular friction member inside the filter barrel, wherein an optical filter can be sandwiched securely inside the filter barrel between the stop structure and the friction member, wherein the friction member is held in place relative to the inner wall by static friction, without any thread, groove, or adhesive.

200. An optical filter wheel module, the module comprising:

an optical filter wheel that is rotatable around a hub structure; and,

a wheel case having a static portion and a removable portion, and at least one set of windows for transmitting light through the wheel case and through a selected optical filter contained in the optical filter wheel, wherein the hub structure is built into the removable portion of the wheel case.

201. The module of claim 200, wherein the wheel case is substantially light-tight, except for light that is transmitted through the windows.

202. The module of claim 200, wherein the windows are in the static portion of the wheel case.

203. The module of claim 200, wherein the windows are in the removable portion of the wheel case.

204. The module of claim 200, wherein the wheel case has a second set of windows, the sets of windows being located on opposite sides of the hub structure, so that any given optical filter in the optical filter wheel can be rotated into alignment with either set of windows.

205. The module of claim 200, further comprising a post-to-hole mating structure that aligns the portions of the wheel case.

206. The module of claim 200, wherein the static portion of the wheel case is fixed to an instrument platform.

207. The module of claim 200, further comprising a driver mechanism configured to rotate the optical filter wheel.

208. A support device for a sample container, the device comprising:

a holder including shelf structure and associated frame structure at least partially defining a generally rectangular area for supporting a microplate, the generally rectangular area being slightly larger than an expected peripheral dimension of the microplate; and

a first releasable clamp mechanism that applies a force against a first side of the microplate, thereby securing the microplate in the holder.

209. The device of claim 208, further comprising a second releasable clamp mechanism that applies a force against a second side of the microplate, thereby securing the microplate in the holder from two sides.

210. The device of claim 209, wherein the first and second releasable clamp mechanisms operate in series.

211. The device of claim 209, wherein the first side of the microplate is perpendicular to the second side of the microplate.

212. The device of claim 208, wherein the first releasable clamp mechanism causes the microplate to be sandwiched between a pusher and an opposing portion of the frame structure.

213. The device of claim 209, wherein portions of the frame structure function as bumpers for the clamp mechanisms.

214. A support device for a sample container, the device comprising:

a holder including shelf structure and associated frame structure at least partially defining a generally rectangular area for supporting a microplate;

wherein the holder has a central opening so that analysis of a sample can be carried out from below the holder; and

wherein the holder has an open end that permits a microplate transfer device to enter the generally rectangular area of the holder.

215. The device of claim 214, further comprising a microplate transfer device that, after moving into the generally rectangular area, can move down relative to the holder, thereby gently dropping the microplate into the generally rectangular area of the holder.

216. A support device for a sample container, the device comprising:

a holder;

a first drive mechanism that moves the holder along an X-axis between a docking station outside an analyzer and an examination site inside the analyzer; and

a second drive mechanism that moves the holder along a y-axis perpendicular to the X-axis when the holder is at the examination site, so that the holder can function both as a sample delivery device in and out of the analyzer, and as a moveable stage for supporting the sample container at the examination site.

217. The device of claim 216, wherein the holder includes shelf structure and associated frame structure at least partially defining a generally rectangular area for supporting a microplate, the generally rectangular area having a central opening so that analysis can be carried out from below the holder when is functioning as a stage at the examination site.

218. A method of automatically feeding microplates in and out of an analyzer, the method comprising:

automatically delivering a microplate just outside an opening to the analyzer;

moving a gripping device from inside the analyzer, through the opening, to a location immediately below the microplate; and

gently dropping the microplate onto the gripping device.

219. The method of claim 218, further comprising clamping the microplate in the holder by applying a first force against a first side of the microplate.

220. The method of claim 219, further comprising clamping the microplate in the holder by applying a second force against a second side of the microplate.

221. The method of claim 220, further comprising serially performing the clamping steps.

222. An apparatus for feeding microplates in and out of an analyzer, the apparatus comprising:

a first station that receives and automatically initiates transport of a microplate into the analyzer for analysis;

a second station where the microplate is handed off to a mover that carries the microplate to and from an examination site inside the analyzer, and

a third station that collects the microplate after examination.

223. The apparatus of claim 222, wherein the first station includes a singulation mechanism configured to separate a microplate from a stack of microplates for transport to the analyzer.

224. The apparatus of claim 223, wherein the stack has a top and bottom, the singulation mechanism taking one microplate at a time from the bottom of the stack.

225. The apparatus of claim 223, wherein the stack has a top and a bottom, the singulation mechanism taking one microplate at a time from the top of the stack.

226. The apparatus of claim 223, further comprising a preprocessing bin positioned at the first station for holding the stack, wherein the preprocessing bin can be removed from the first station and replaced with another preprocessing bin containing a new stack of microplates with samples to be analyzed.

227. The apparatus of claim 222, wherein the second station includes a stacking mechanism that adds a microplate to a stack of microplates.

228. The apparatus of claim 227, wherein the stack has a top and bottom, the stacking mechanism adding one microplate at a time to the bottom of the stack.

229. The apparatus of claim 227, wherein the stack has a top and a bottom, the stacking mechanism adding one microplate at a time to the top of the stack.

230. The apparatus of claim 227, further comprising a postprocessing bin positioned at the second station for holding the stack, wherein the postprocessing bin can be removed from the second station and replaced with another postprocessing bin containing a new stack of microplates with samples to be analyzed.

231. The apparatus of claim 222, further comprising a tray that carries a microplate between stations.

232. The apparatus of claim 231, further comprising a microplate stacking and destacking device operatively associated with the tray, the stacking and destacking device moving with the tray and being capable of taking a microplate one at a time from a first stack of microplates at the first station, handing off the microplate to the mover, which carries the microplate to and from an examination site inside the analyzer, and adding the microplate to a second stack of microplates at the third station after analysis.

233. The apparatus of claim 232, wherein the stacking and destacking device includes a lifter and a latch that cooperate to remove a microplate from the first stack, and to add a microplate to the second stack.

234. The apparatus of claim 231, wherein the first station has a dedicated first handler that takes a microplate from a first stack of microplates and deposits the microplate on the tray, the second station has a second handler that hands-off the microplate from the tray to the mover, which carries the microplate to and from an examination site inside the analyzer, and the third station has a third handler that transfers the microplate from the tray to a second stack of microplates after analysis.

235. The apparatus of claim 234, wherein each handler at the first and third stations includes a lifter and a latch that cooperate to transfer a microplate to or from a stack.

236. The apparatus of claim 222, wherein a first linear path connects the examination site to the second station, and a second linear path connects the first, second and third stations, the first linear path being substantially perpendicular to the second linear path.

237. The apparatus of claim 222, wherein the examination site and the first, second, and third stations all are positioned along a single substantially linear path.

238. A microplate handling device for handling a microplate, the device comprising:

a lifter configured to raise or lower a microplate relative to the bottom of a stack of microplates; and

at least one latch having a pick portion, the latch being mounted so that the pick portion moves in and out of gaps between adjacently stacked microplates in response to up and down movement of the lifter.

239. The device of claim 238, further comprising

a second lifter arranged so that the lifters support opposite sides of a microplate.

240. The device of claim 238, further comprising three additional latches, the latches being positioned near four corners of the bottom of a stack of microplates.

241. The device of claim 238, wherein the lifter and latch are designed to remove a single microplate from the bottom of a stack of microplates, so that the lifter pushes the latch completely out from under the stack as it moves up to support a microplate positioned at the bottom of the stack.

242. The device of claim 238, wherein the lifter and latch are designed to add a microplate to the bottom of a stack of microplates, so that the latch is pushed out of the way by the microplate being pushed up by the lifter until the microplate is high enough for the latch to move inward and underneath the microplate, thereby supporting the stack.

243. The device of claim 238, wherein the latch has a pick portion that is urged laterally toward the bottom of the stack.

244. The device of claim 243, wherein the pick portion is urged toward the bottom of the stack by configuring the latch so that a center of gravity is positioned upward and toward the stack relative to a pivot point.

245. The device of claim 243, wherein the pick portion is urged toward the bottom of the stack by a spring.

246. An automated analyzer system, the system comprising:

an analyzer unit having an internal examination site; and

first and second external loading stations, the first external loading station configured to receive a microplate before analysis, the second external loading station configured to receive the microplate after analysis.

247. The system of claim 246, further comprising a robot programmed to deliver a microplate to the first external loading station, and to retrieve a different microplate from the second loading station in the same trip.

248. The system of claim 246, wherein the loading stations are adjacent one another.

249. The system of claim 246, further comprising a third station, wherein one of the stations receives and automatically initiates transport of a microplate into the analyzer for analysis, another station facilitates hand-off of a microplate to a mover that carries the microplate to and from an examination site inside the analyzer, and the other station collects the microplate after examination.

250. A device for controlling an analyzer, the device comprising:

a plurality of control interface docking locations disposed on a housing containing the analyzer; and

a control unit that can be mounted at any one of the docking locations, so that a user can control the analyzer by inputting information through the control unit;

wherein the control unit can be moved from one docking location to another to provide convenience in different modes of operation.

251. The device of claim 250, wherein the control unit includes data input and output components.

252. The device of claim 250, wherein the control unit is L-shaped and configured to mount on a top edge of the housing.

253. The device of claim 250, wherein the control unit has a horizontal panel portion for resting on a top portion of the housing, and a vertical panel portion for resting against a side portion of the housing adjacent the top portion.

254. The device of claim 253, wherein an inner side of one of the panels has mating structure that compliments other mating structure provided at each of the docking locations.

255. The device of claim 250, wherein the housing has a sample input side, a first docking location being located near an upper edge of the sample input side.

256. The device of claim 255, wherein the housing has a back side opposite the sample input side, a second docking location being located near an upper edge of the back side of the housing.

257. The device of claim 250, wherein the control unit has a front face containing a display screen for indicating instrument status data.

258. The device of claim 257, wherein the front face of the control unit contains at least one data input button for carrying-out one or more of the following command functions: start, reset, load, and eject.

259. The device of claim 257, wherein the front face of the control unit contains at least one light indicator for indicating one or more of the following data output functions: power, fault, and service required.

260. A device for controlling an analyzer, comprising

a first control interface docking location on or near an upper edge of a first side of a housing containing the analyzer, wherein the first side also includes a sample input port; and

a control unit that can be operatively mounted at the first control interface docking location;

wherein the control unit can be operatively relocated at a second control interface docking location remote from the first side of the housing.

261. The device of claim 260, wherein the second control interface docking location is located on or near a second side of the housing.

262. The device of claim 260, wherein the second control interface docking location is spaced apart from the housing.

263. The device of claim 260, further comprising a second control unit, wherein a user can control the analyzer by inputting information through either control unit.

264. A method of controlling an analyzer capable of being used in a manual mode or a robotic mode, the method comprising:

providing a control unit that can be mounted at a first or second docking location, wherein the docking locations are disposed on a housing containing the analyzer;

mounting the control unit in the first docking location when the analyzer is to be used in the manual mode; and

mounting the control unit in the second docking location when the analyzer is to be used in the robotic mode.

265. An apparatus for measuring the polarization of luminescence emitted from a sample, the apparatus comprising:

a stage for supporting a composition at an examination site;

a time-varying light source and a first excitation optical relay structure that includes a first excitation polarizer, wherein the first excitation optical relay structure directs light from the time-varying light source through the first excitation polarizer toward the composition;

a continuous light source and a second optical relay structure that includes a second excitation polarizer, wherein the second excitation optical relay structure directs light from the time-varying light source through the second excitation polarizer toward the composition;

a detector and an emission optical relay structure that includes an emission polarizer, wherein the emission optical relay structure directs light from the composition through the emission polarizer toward the composition; and

a switching mechanism for interchangeably connecting different light sources to the optical relay structure for different applications.

266. The apparatus of claim 265, wherein the first and second excitation polarizers are the same.

267. The apparatus of claim 265, wherein the continuous light source includes the first excitation polarizer.

268. The apparatus of claim 265, wherein the time-varying source is dedicated to time-resolved fluorescence polarization measurements, and the continuous source is dedicated to steady-state polarization measurements.

269. The apparatus of claim 265, wherein the continuous light source is a high color-temperature xenon arc lamp.

270. An apparatus for measuring the polarization of luminescence emitted from a sample, the apparatus comprising:

a stage configured to hold a microplate having an array of sample wells;

a continuous light source and an excitation optical relay structure that directs light from the continuous light source through an excitation polarizer toward the composition; and

a detector and an emission optical relay structure that directs light from the composition through an emission polarizer toward the detector.

271. A method of quantifying an optical signal, the method comprising:

integrating current from a detector until a threshold charge is collected;

measuring the time period that it takes to collect the threshold charge; and

determining the magnitude of the optical signal based on the measured time period.

272. The method of claim 271, wherein the detector is a photomultiplier tube.

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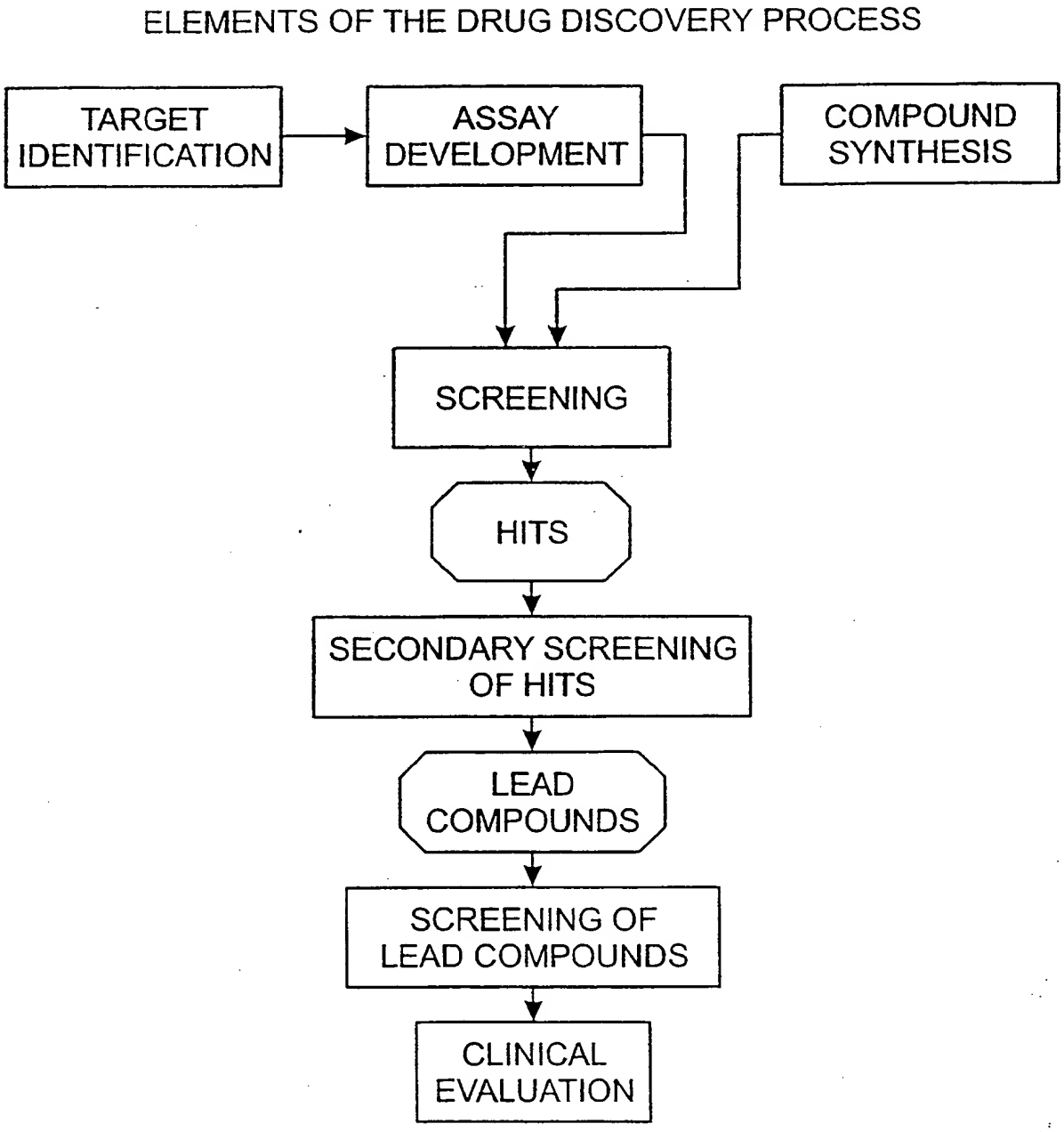
Fig. 1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ASSAY DEVELOPMENT
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CLINICAL EVALUATION

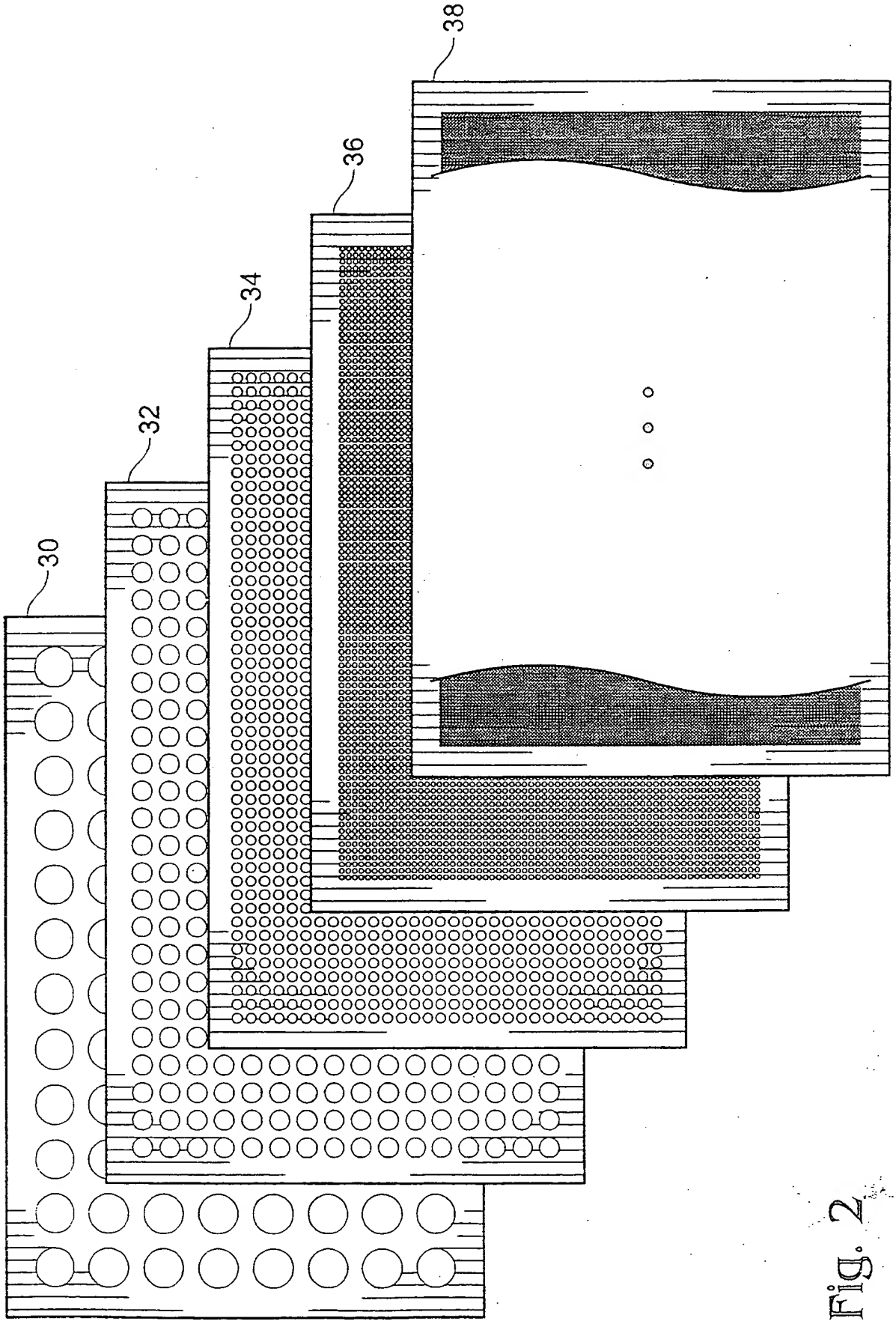
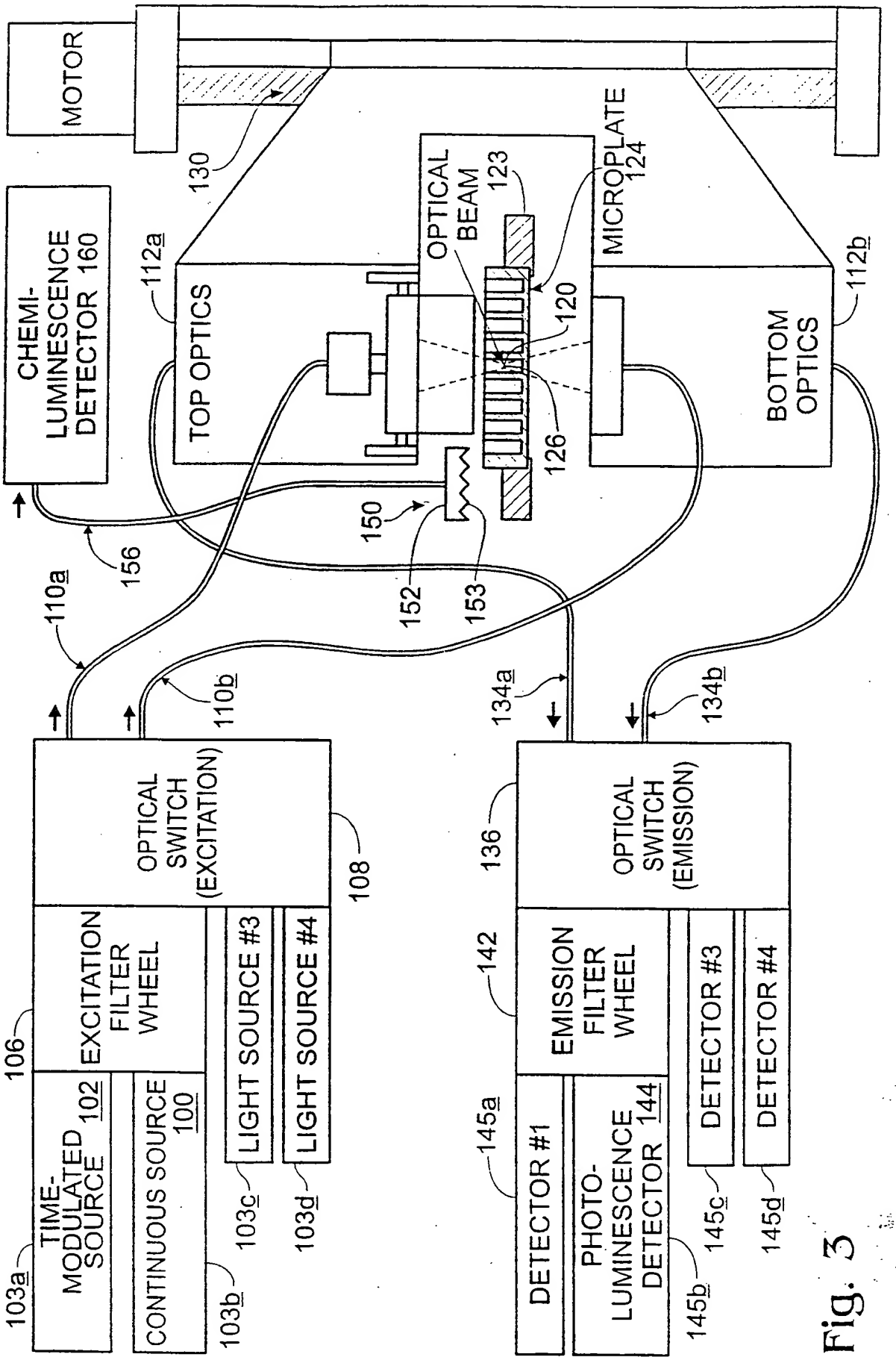


Fig. 2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BOTTOM OPTICS
112b
150
152
153
156
110a
110b
134a
134b
OPTICAL SWITCH (EXCITATION)
108
OPTICAL SWITCH (EMISSION)
136
106
EXCITATION FILTER WHEEL
142
EMISSION FILTER WHEEL
TIME-MODULATED SOURCE 102
CONTINUOUS SOURCE 100
LIGHT SOURCE #3
LIGHT SOURCE #4
DETECTOR #1
PHOTO-LUMINESCENCE DETECTOR 144
DETECTOR #3
DETECTOR #4
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103d
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Fig. 3

Fig. 4

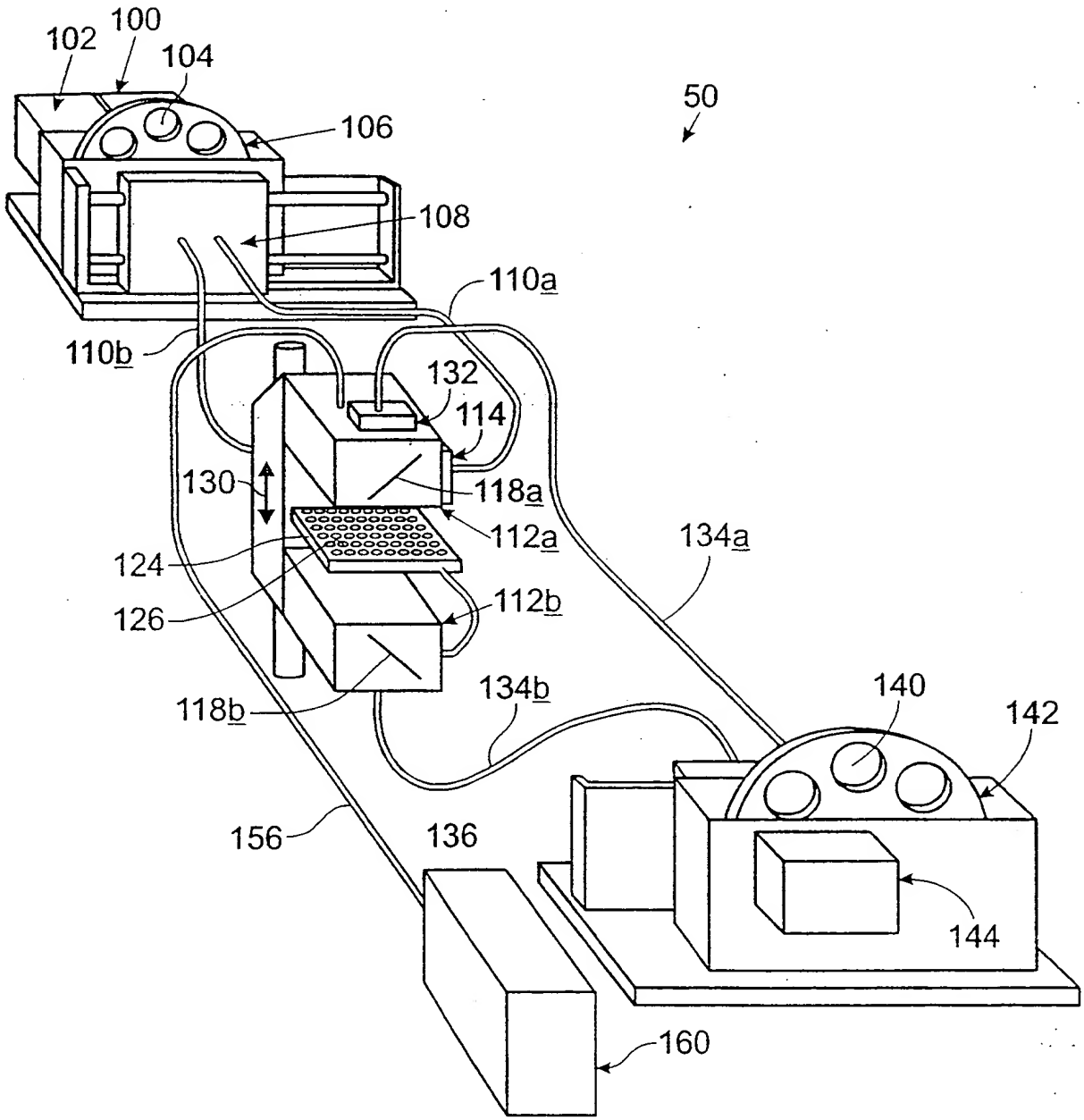
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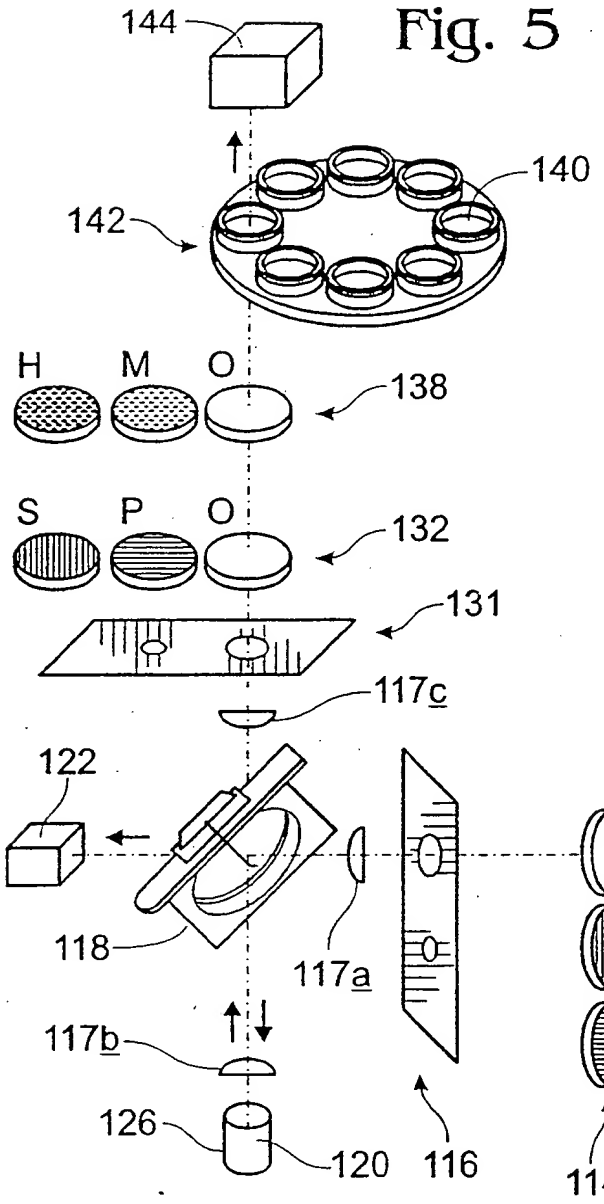
Fig. 5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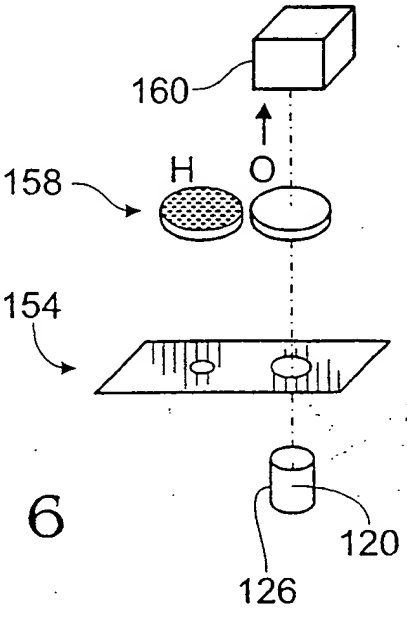
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Fig. 6

Fig. 7

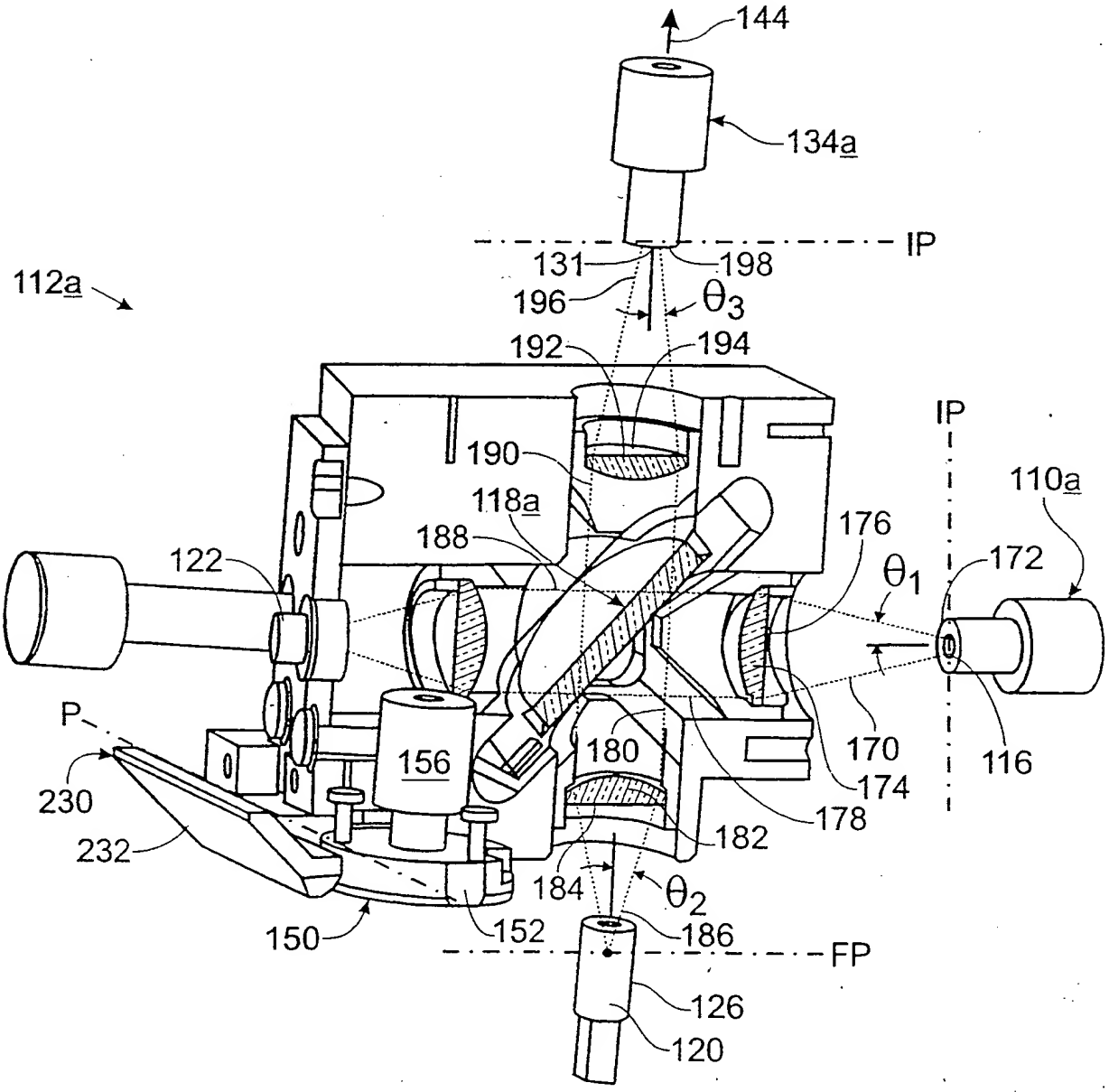
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Fig. 8

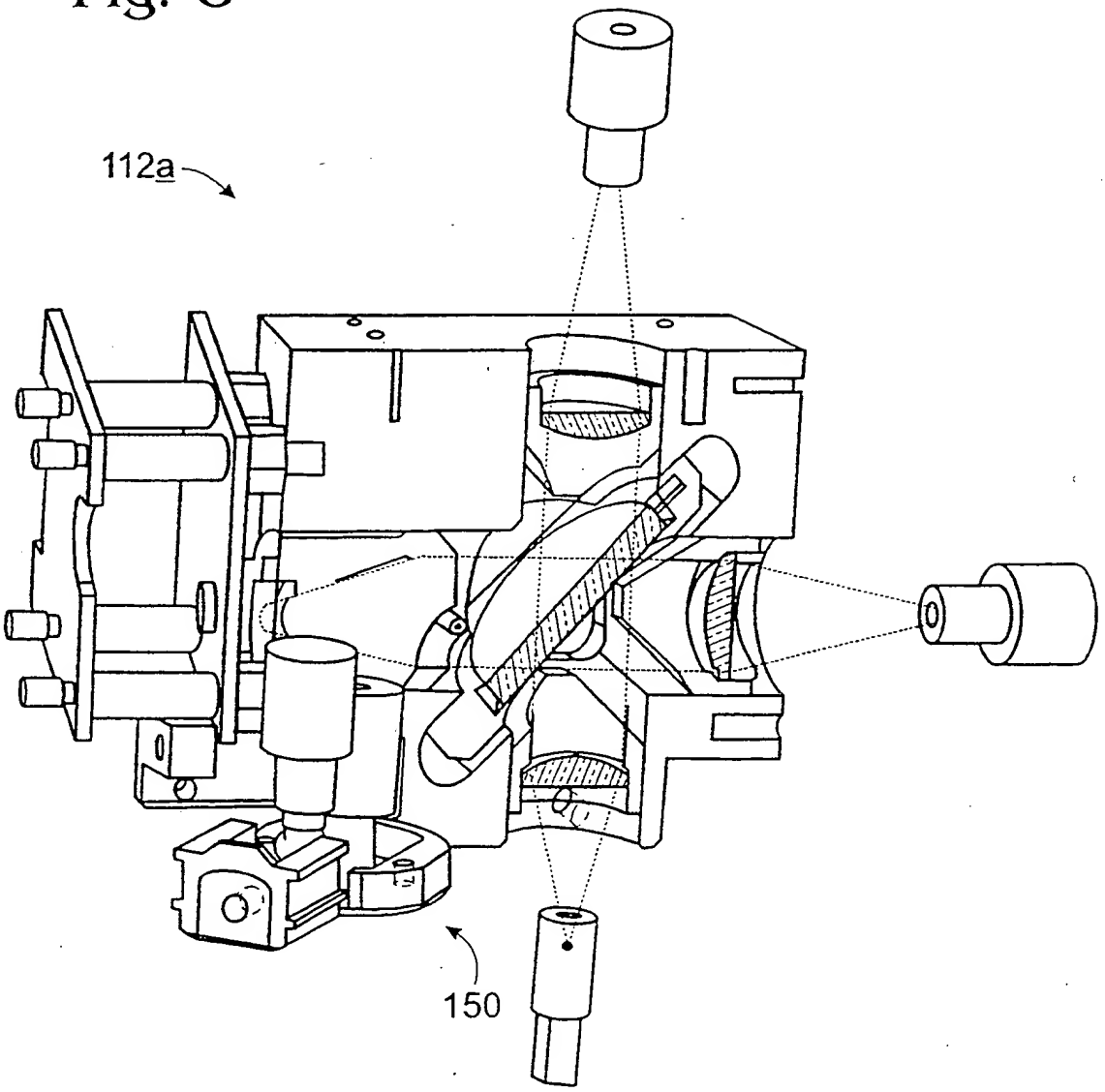


Fig. 9

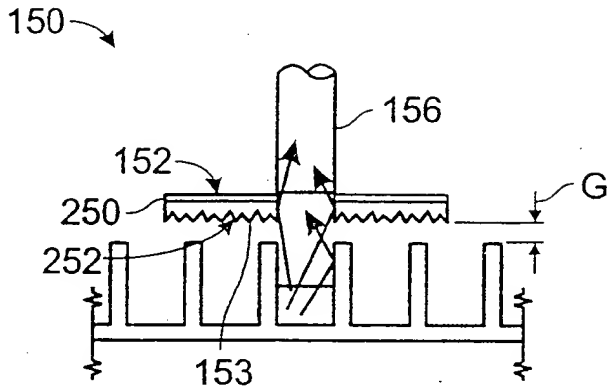


Fig. 10

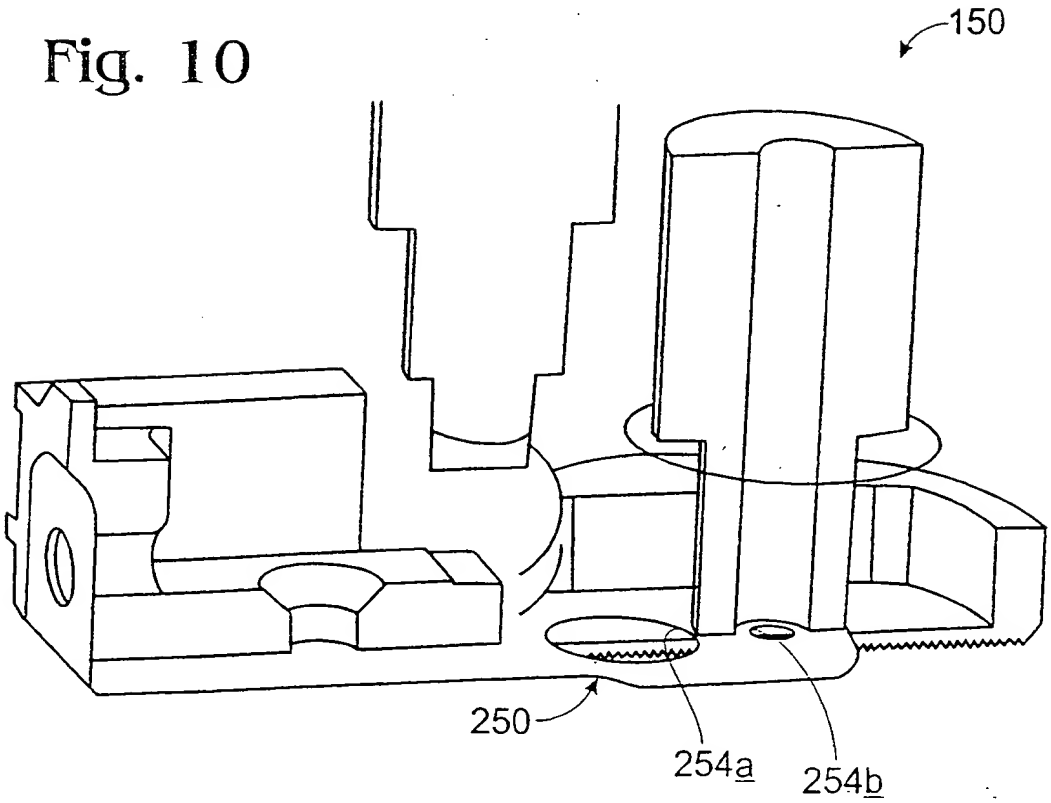


Fig. 11

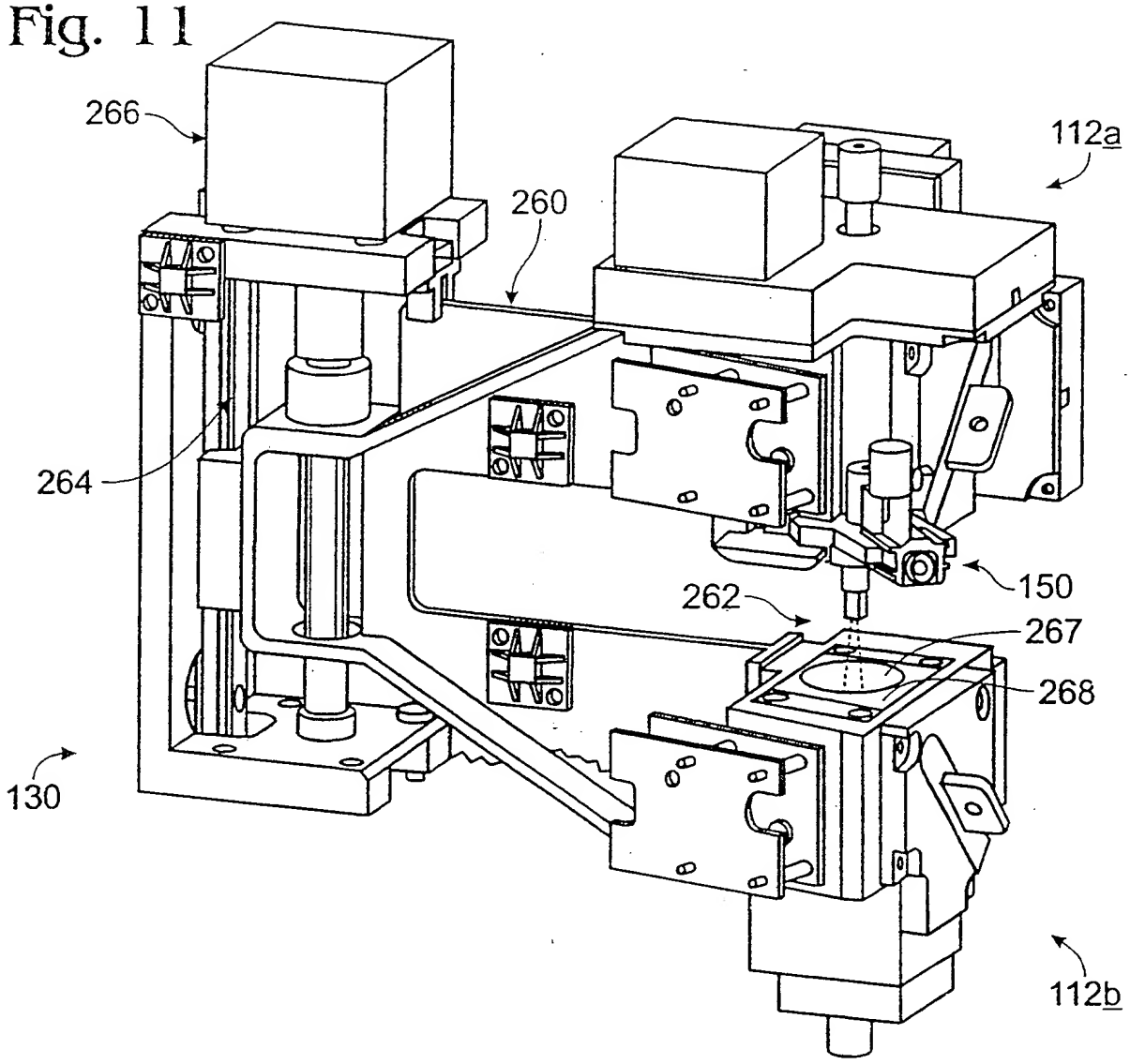


Fig. 12

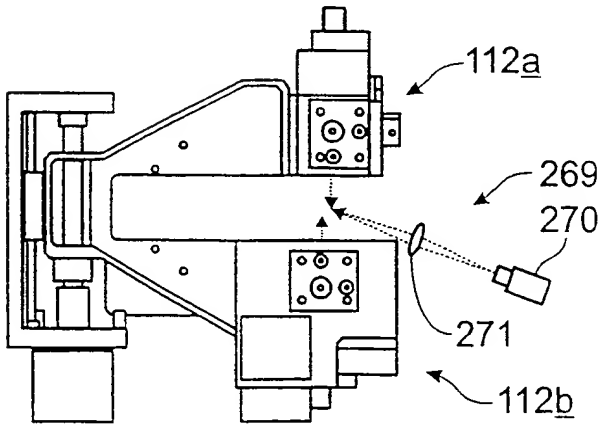
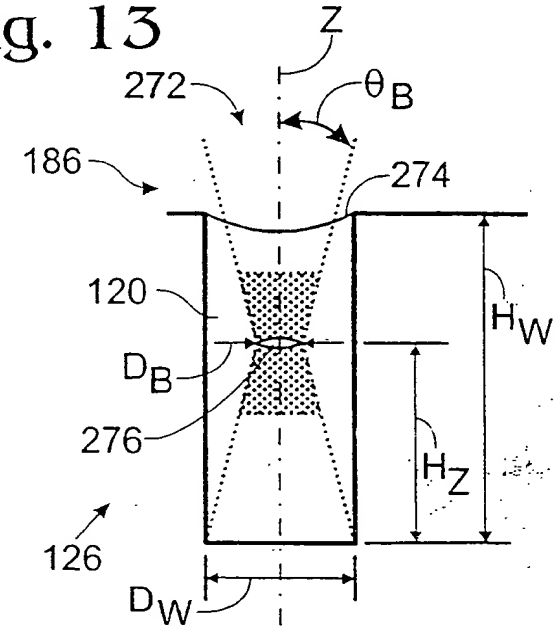


Fig. 13



Not to be taken into consideration for international processing.

Any reference to Figures 14 and 15 shall be considered non existent Article 14(2).

Fig. 16

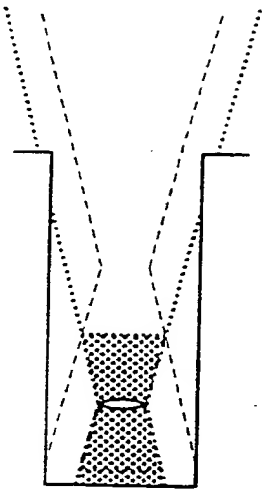


Fig. 17

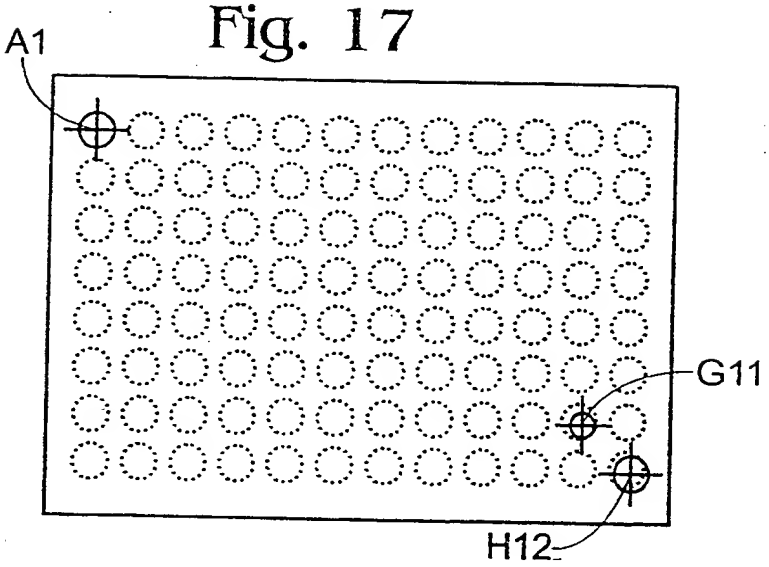


Fig. 18

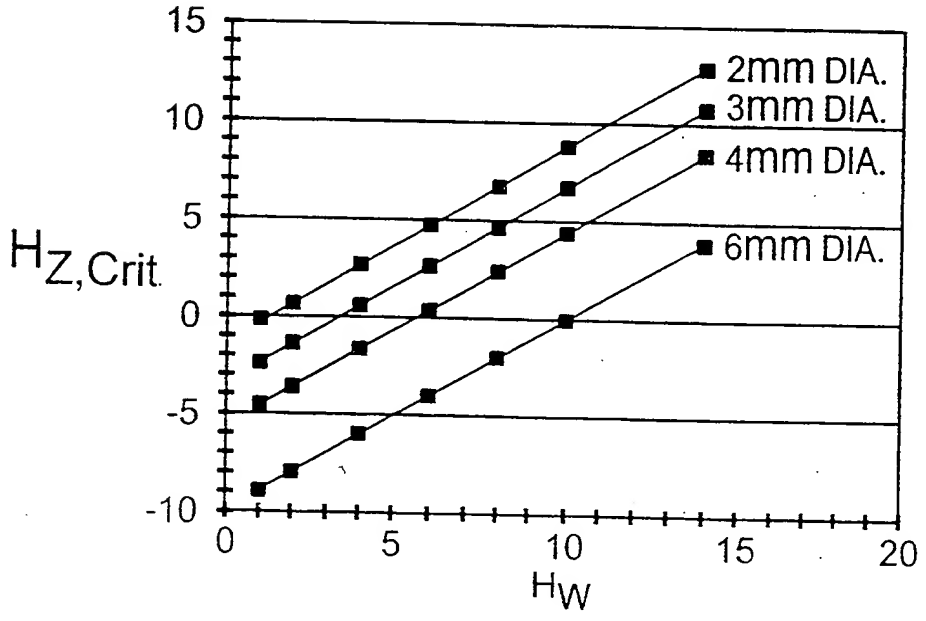
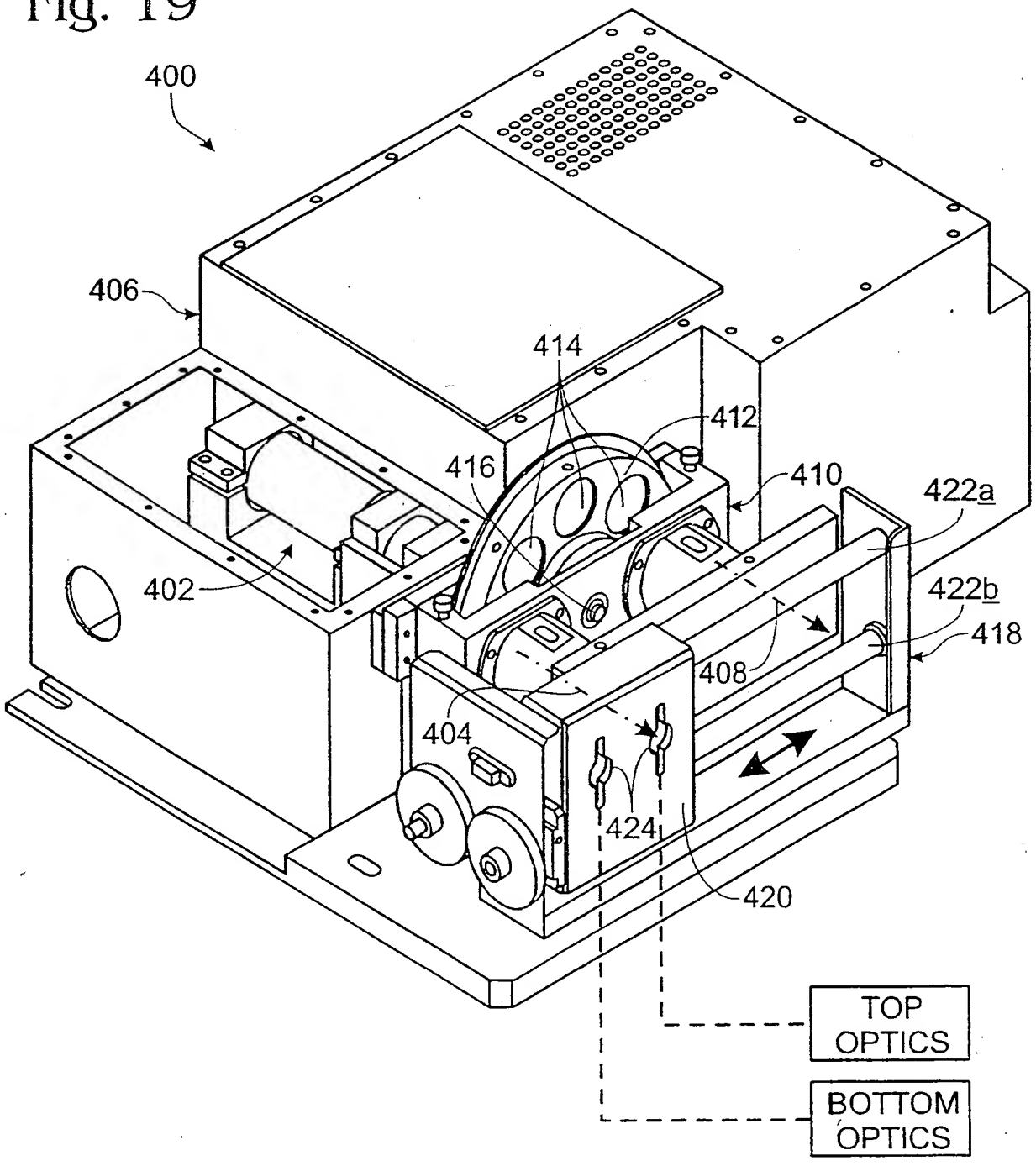


Fig. 19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TOP OPTICS
BOTTOM OPTICS

Fig. 20

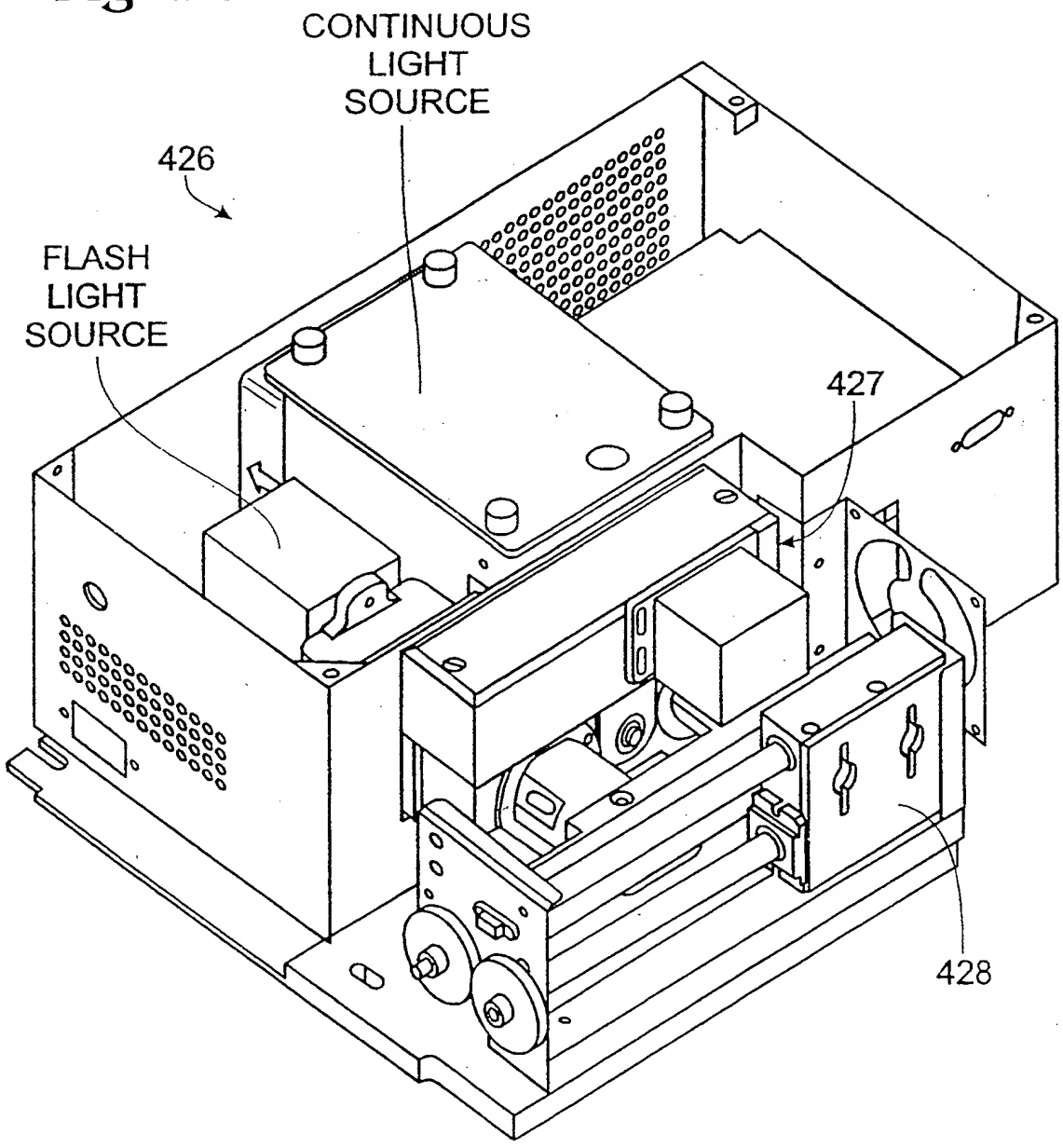

Fig. 21

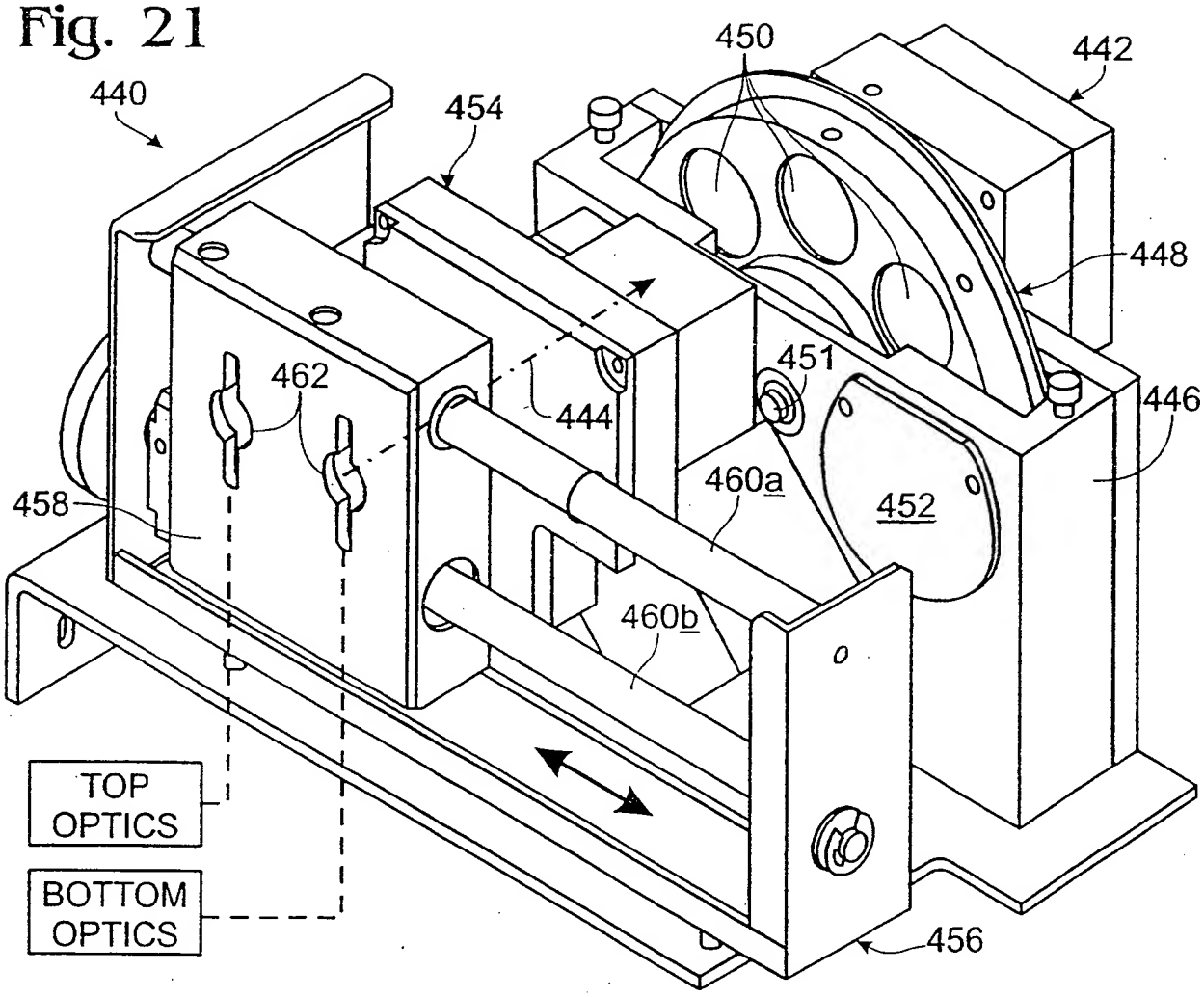
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Fig. 22

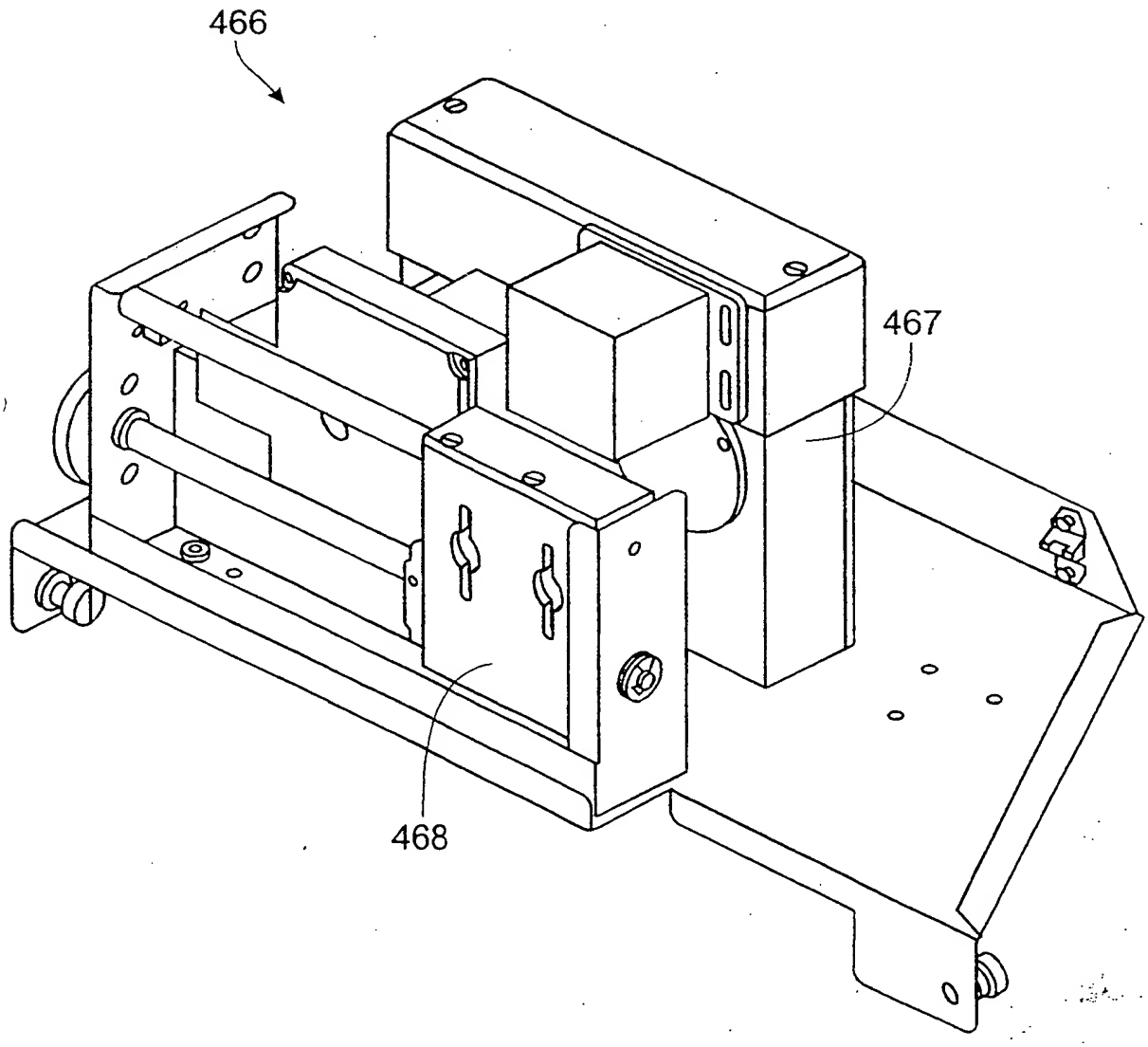

Fig. 23

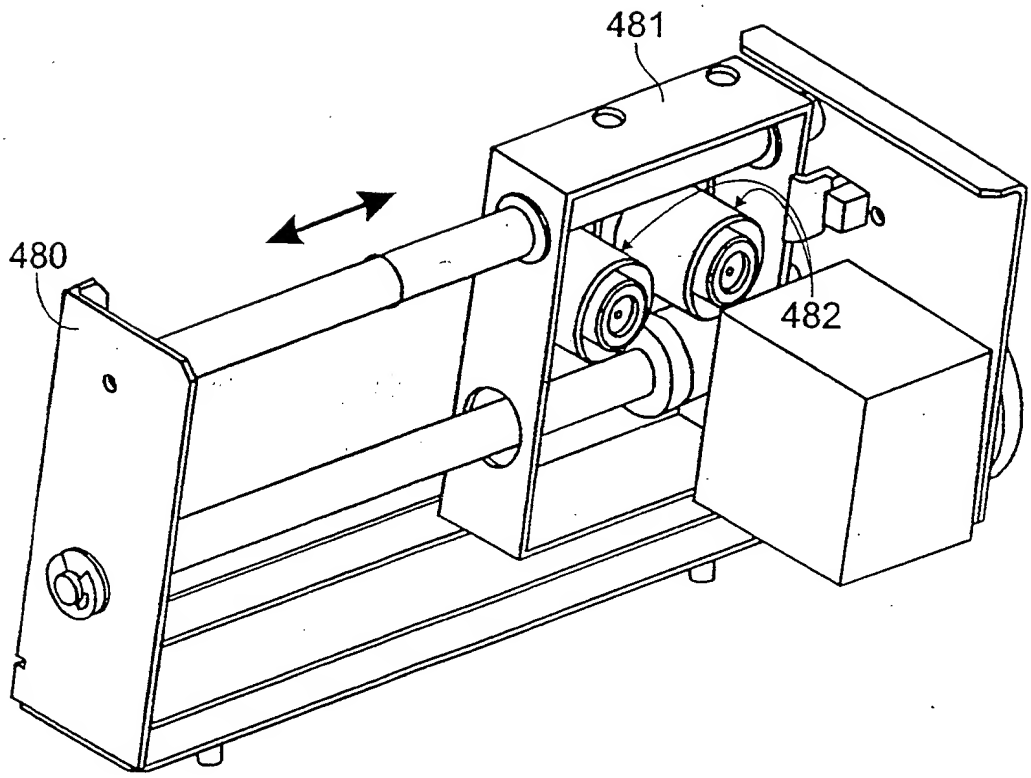

Fig. 24

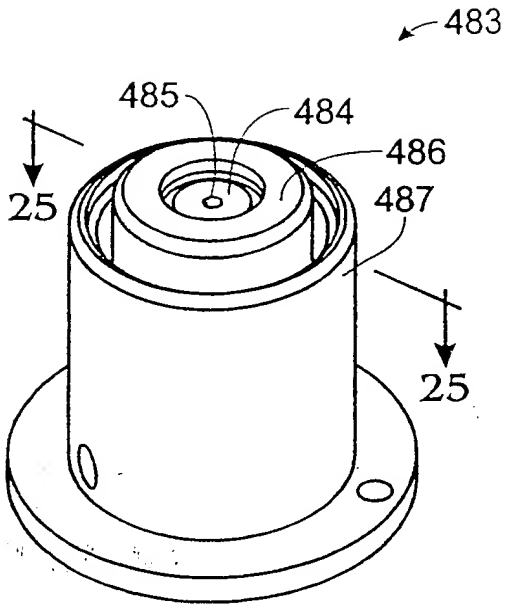
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Fig. 25

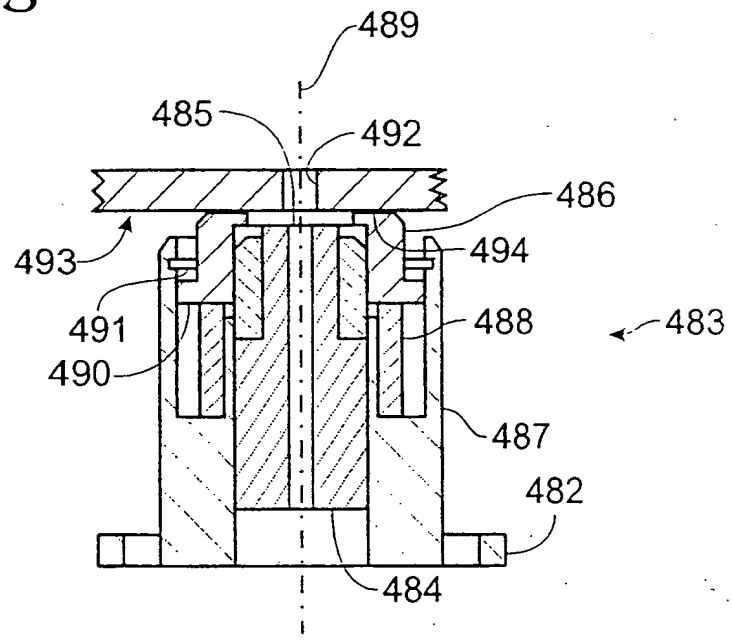
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Fig. 26

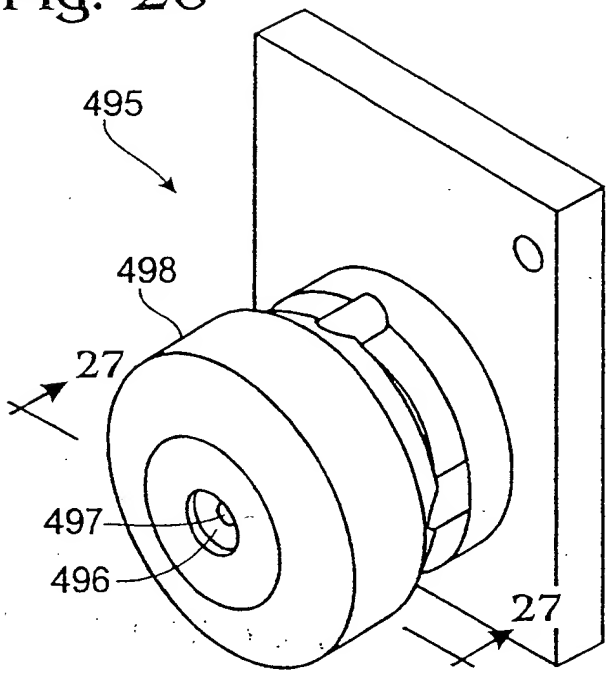
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Fig. 27

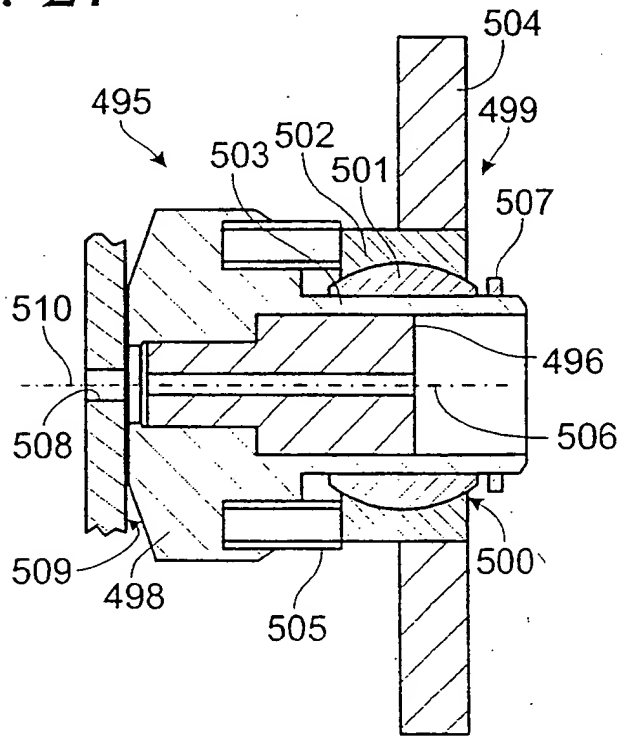
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Fig. 28

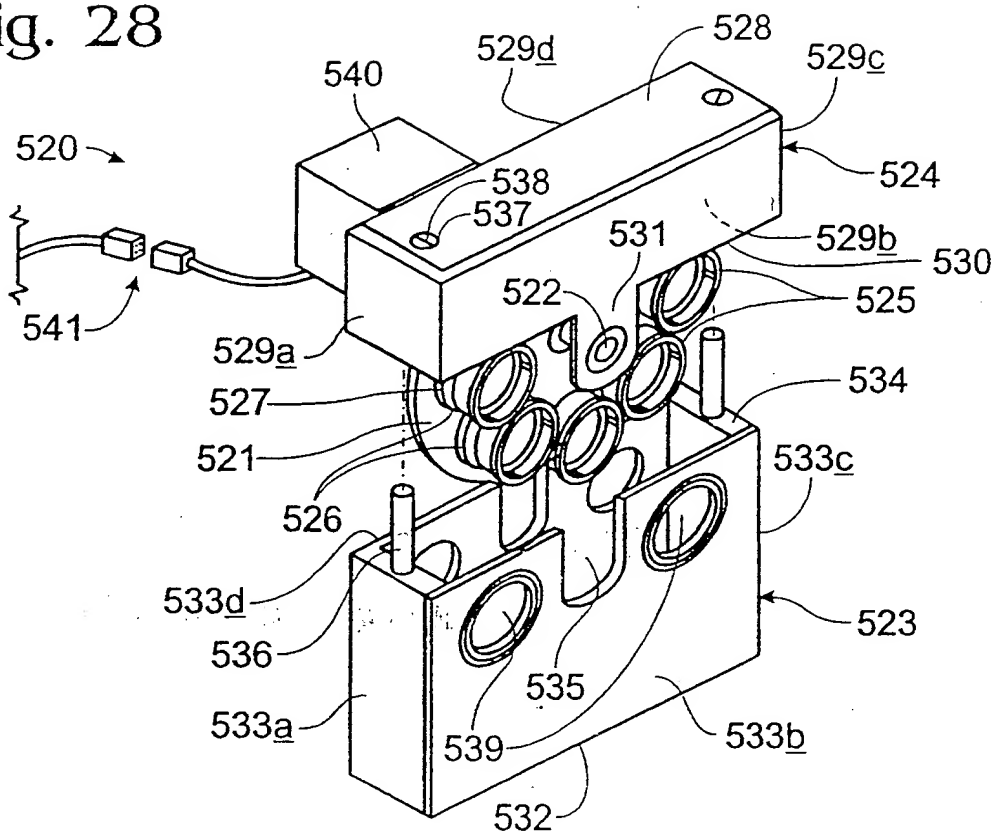
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Fig. 29

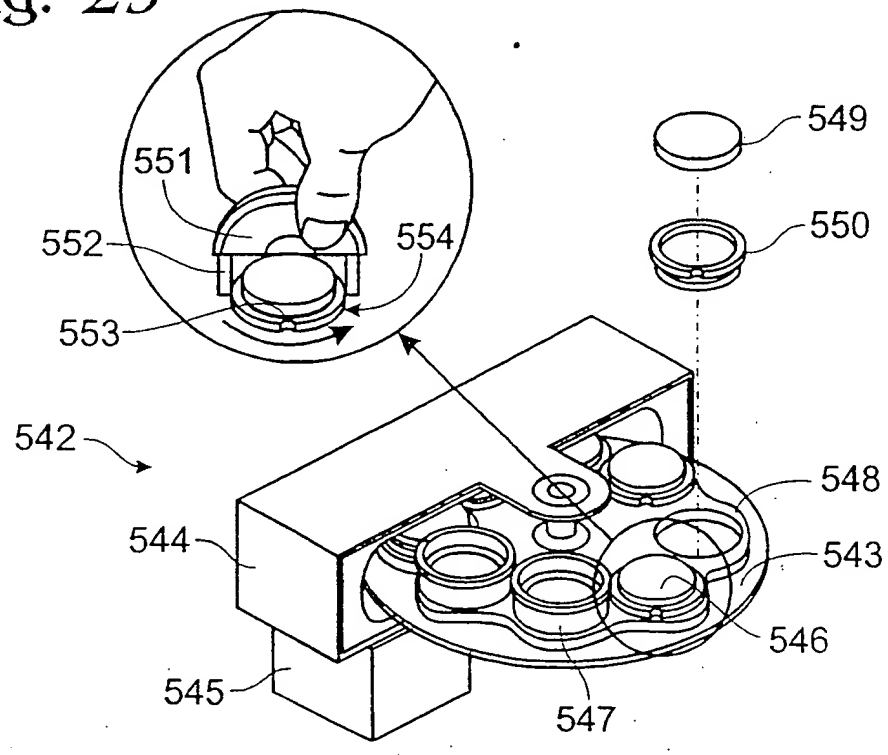
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Fig. 30

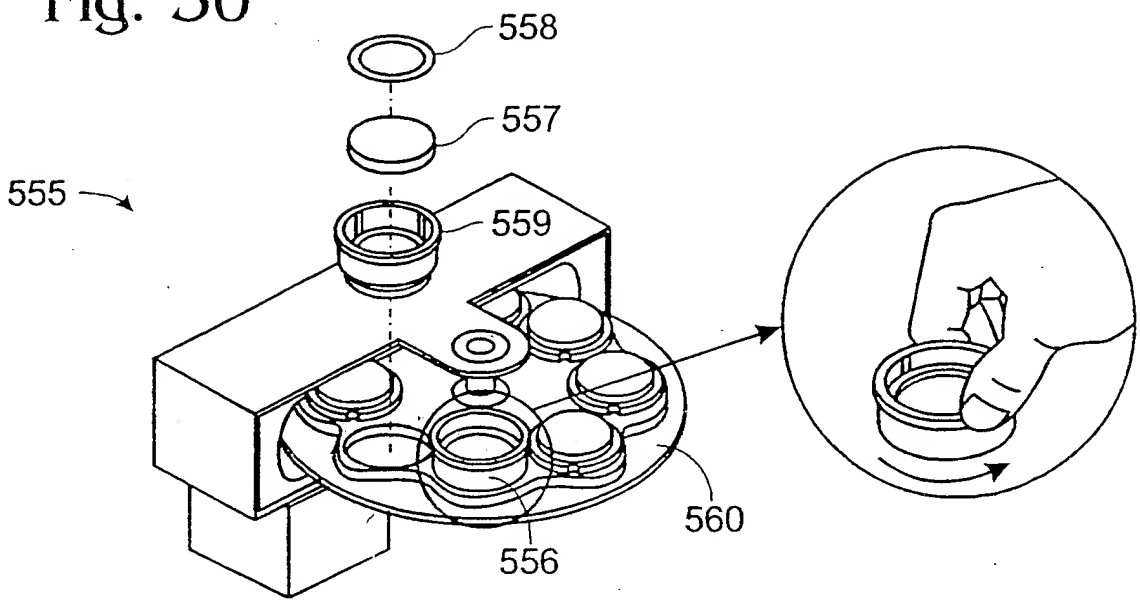


Fig. 31

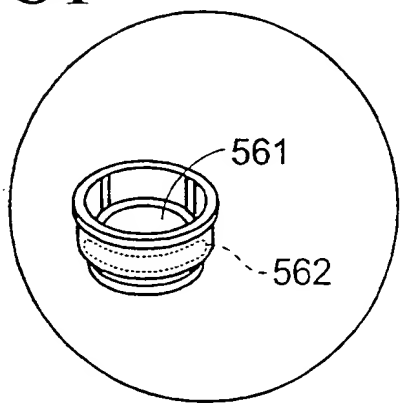


Fig. 32

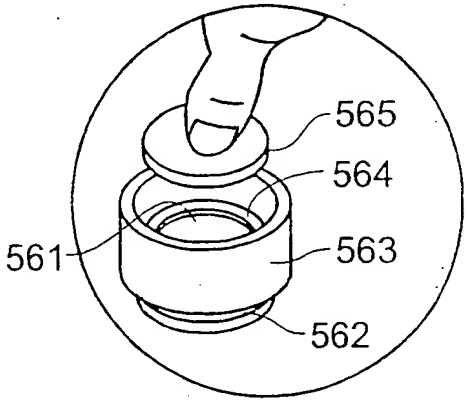


Fig. 33

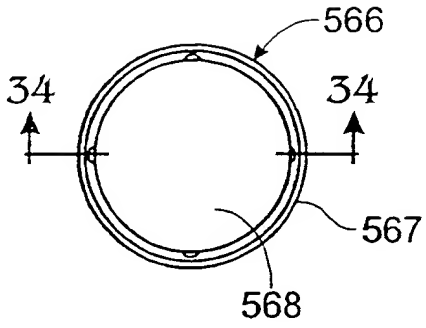


Fig. 34

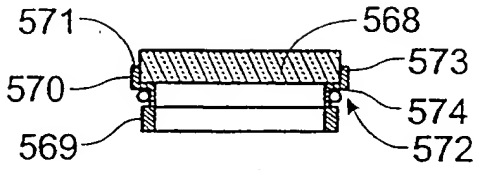


Fig. 35

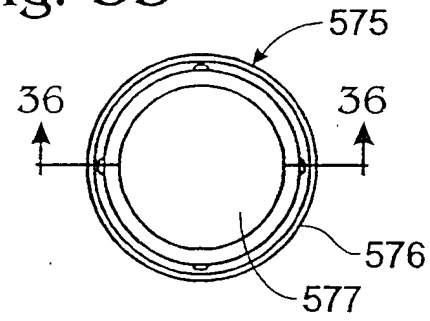


Fig. 36

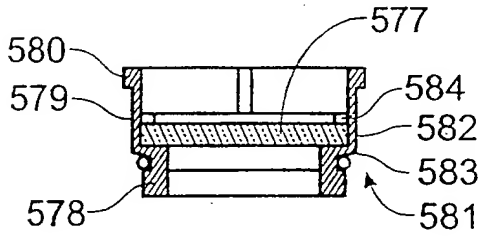


Fig. 37

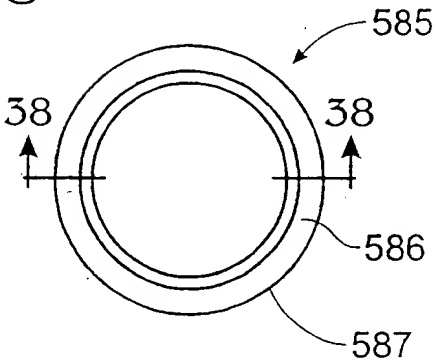


Fig. 38

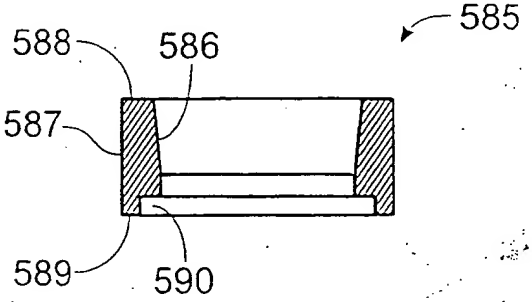
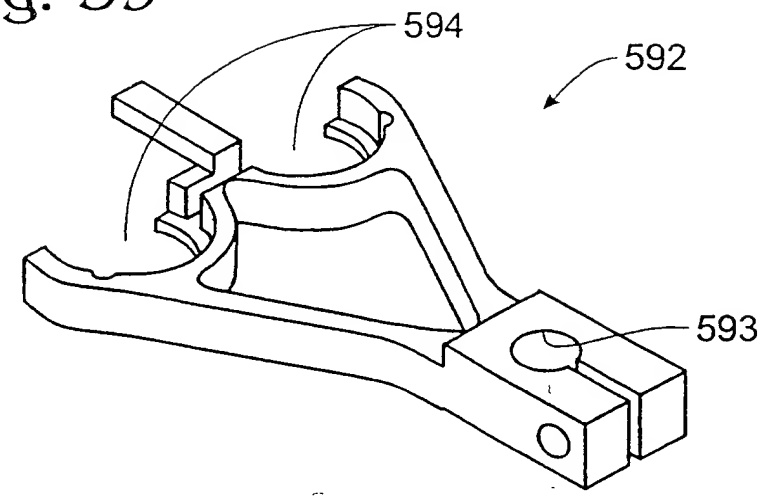


Fig. 39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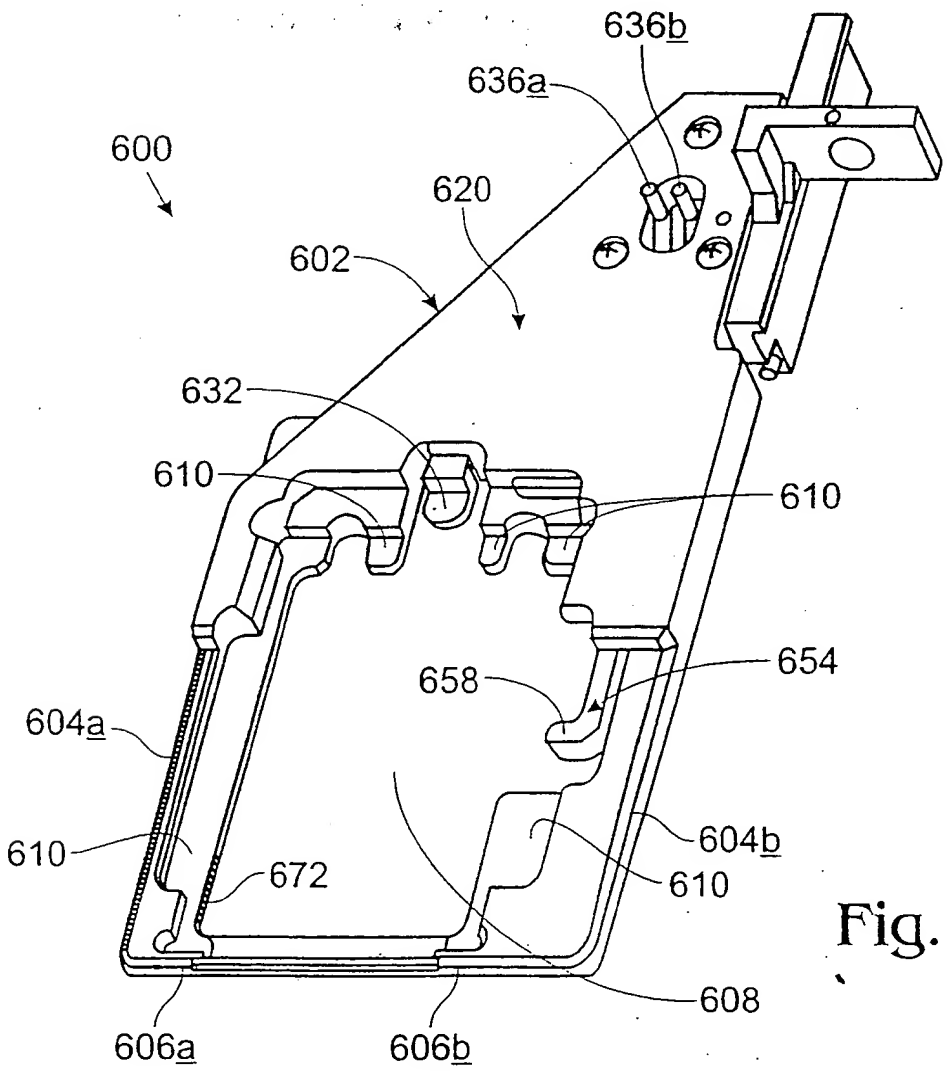
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Fig. 40

Fig. 41

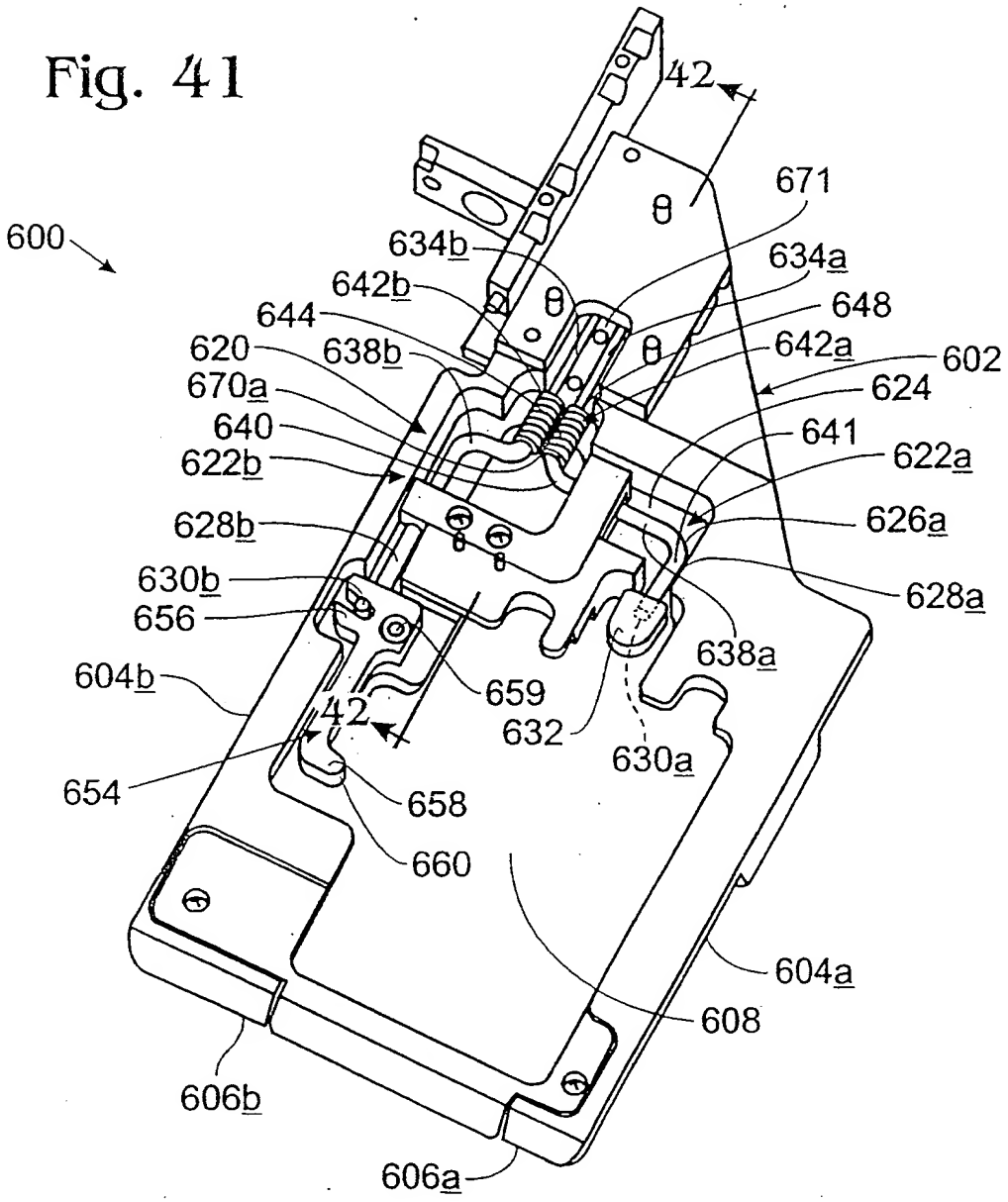
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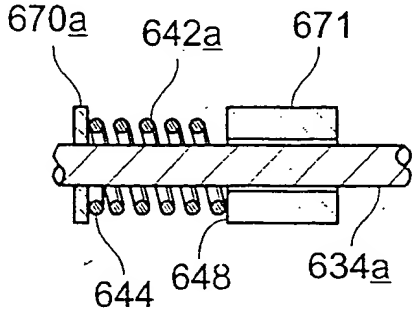
Fig. 42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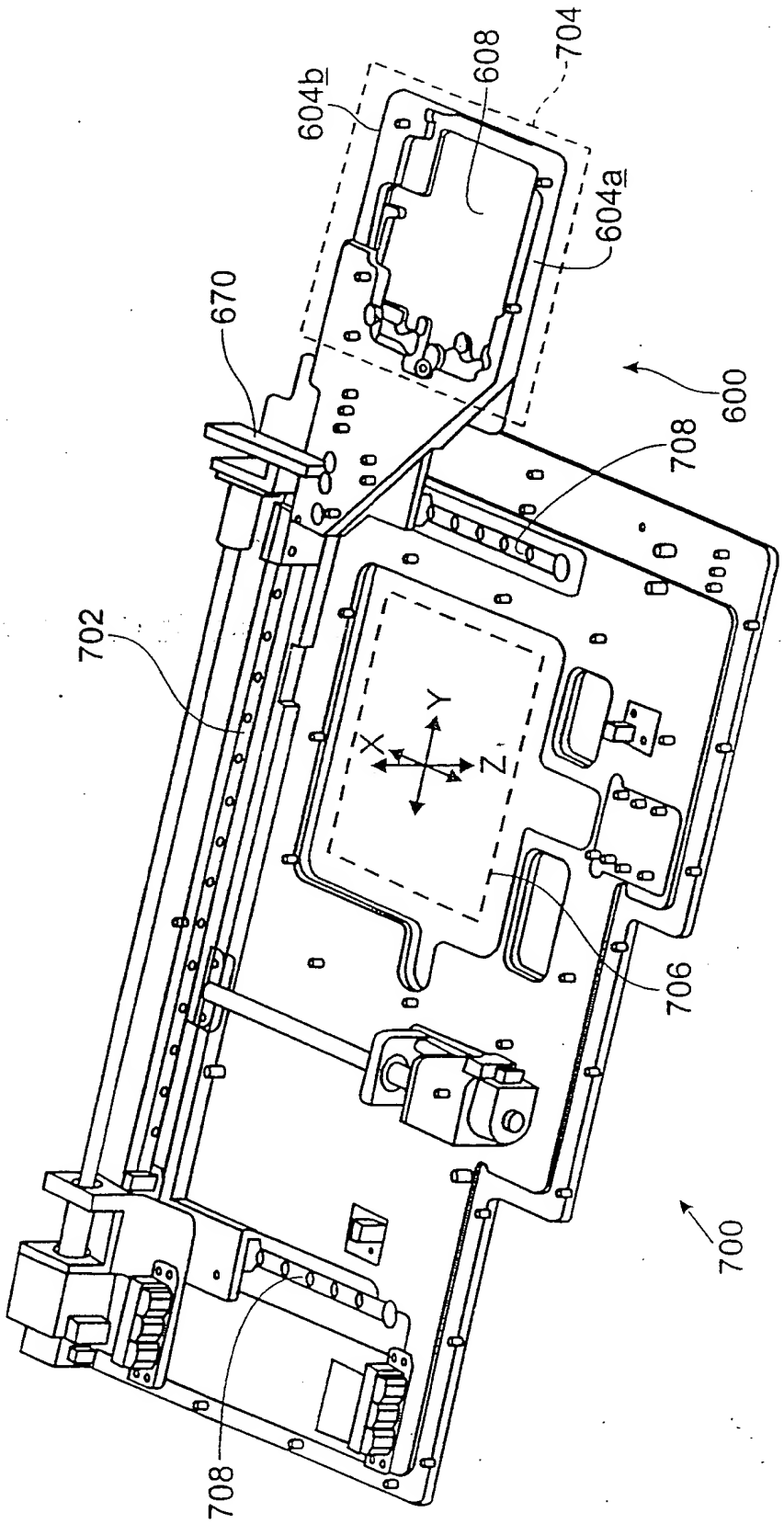

Fig. 43

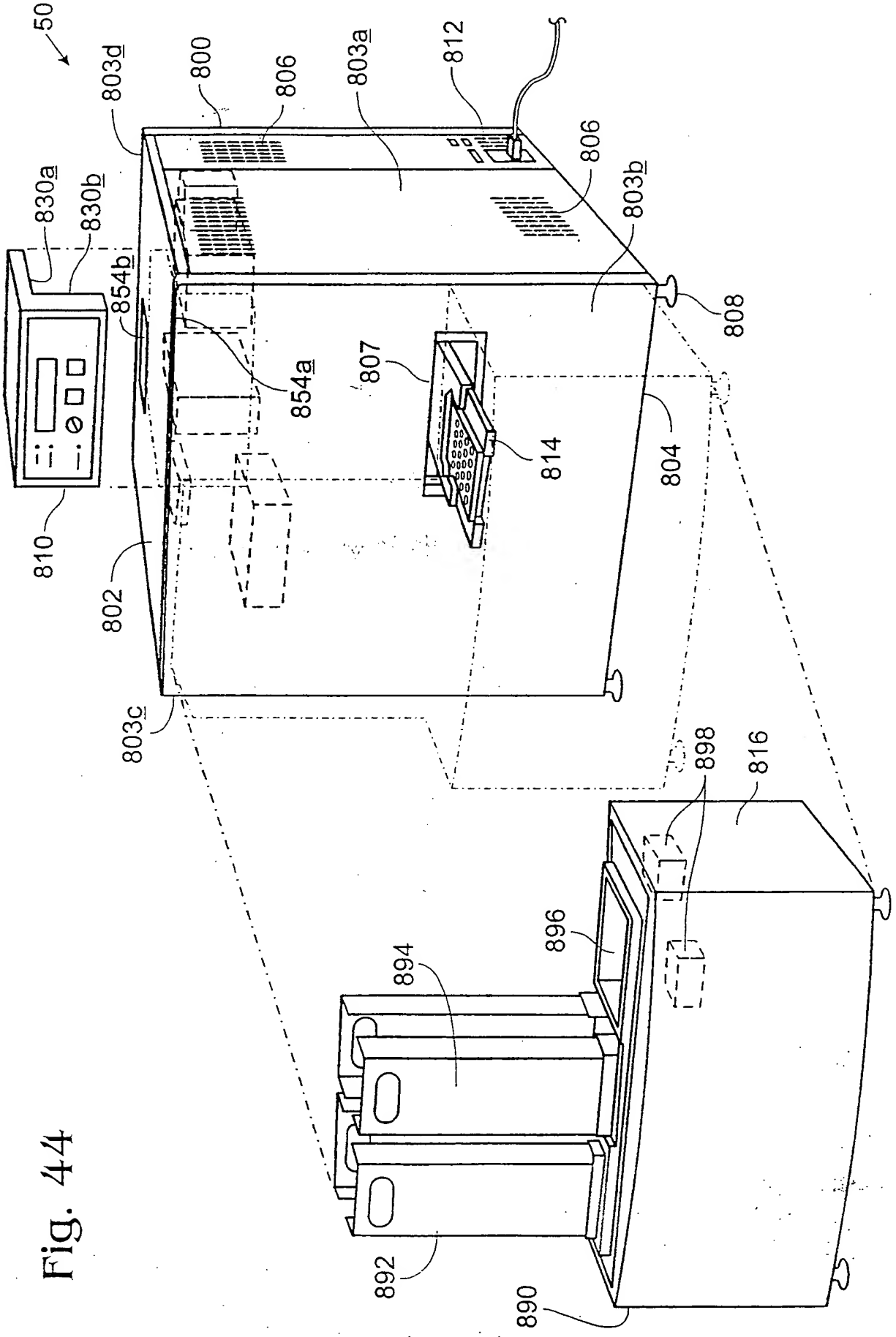
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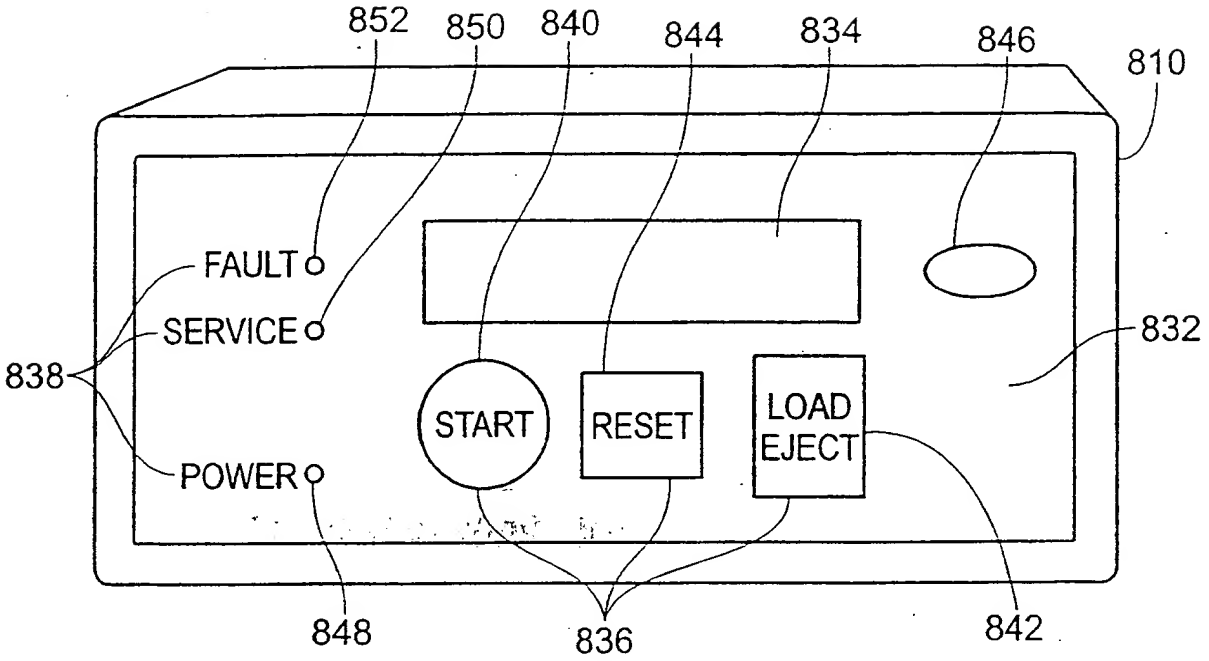
Fig. 44

Fig. 45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SERVICE
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START
RESET
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EJECT
POWER
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Fig. 46

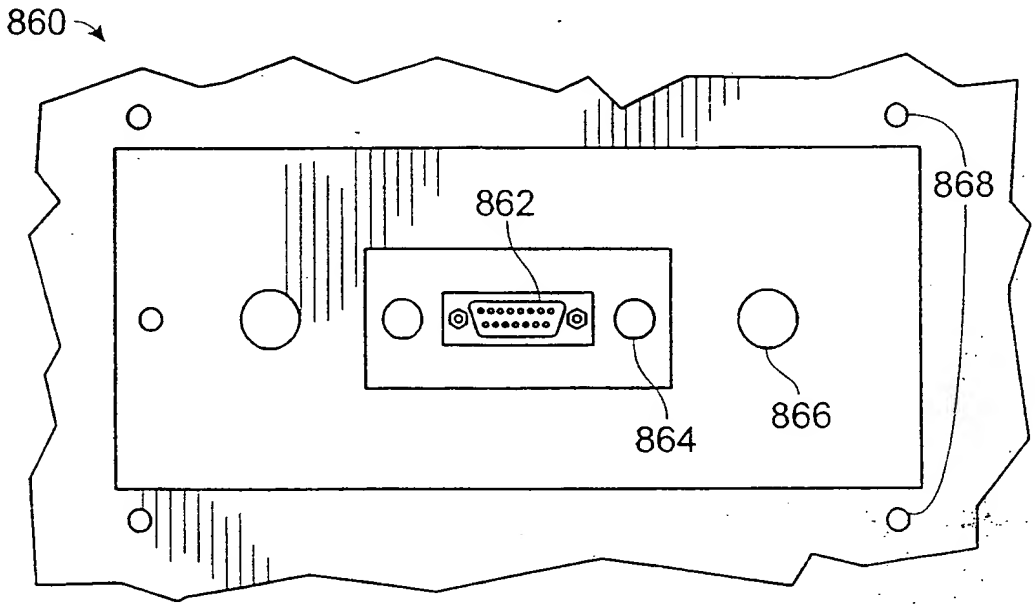
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Fig. 47

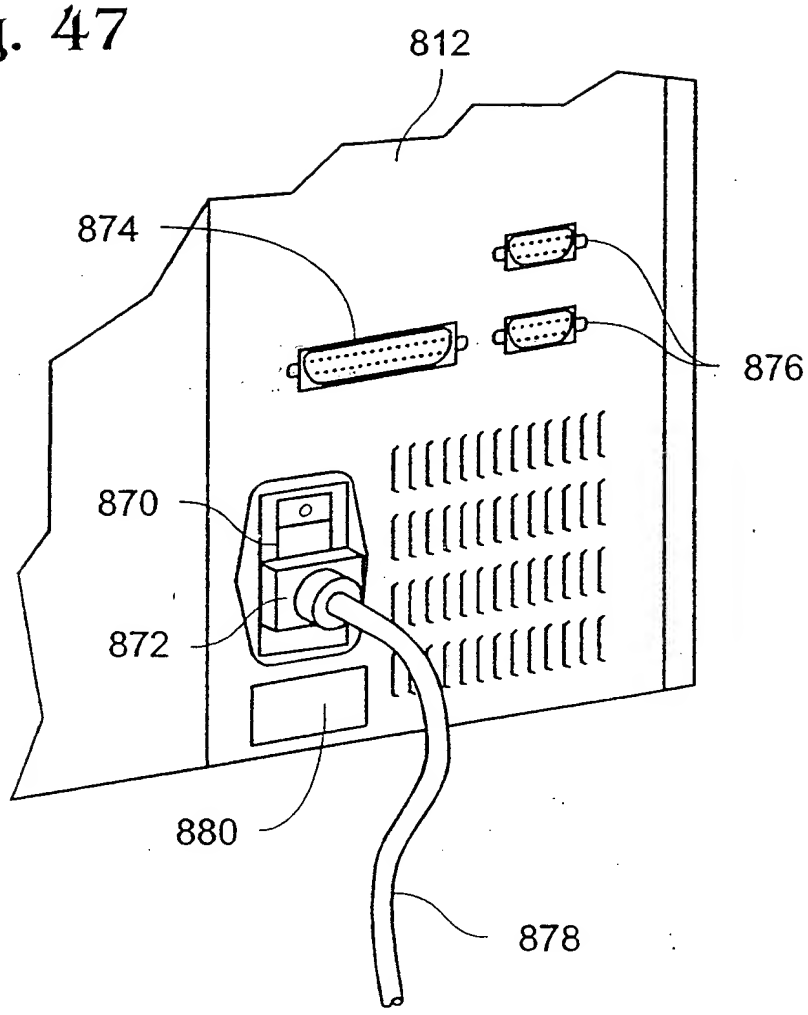


Fig. 48

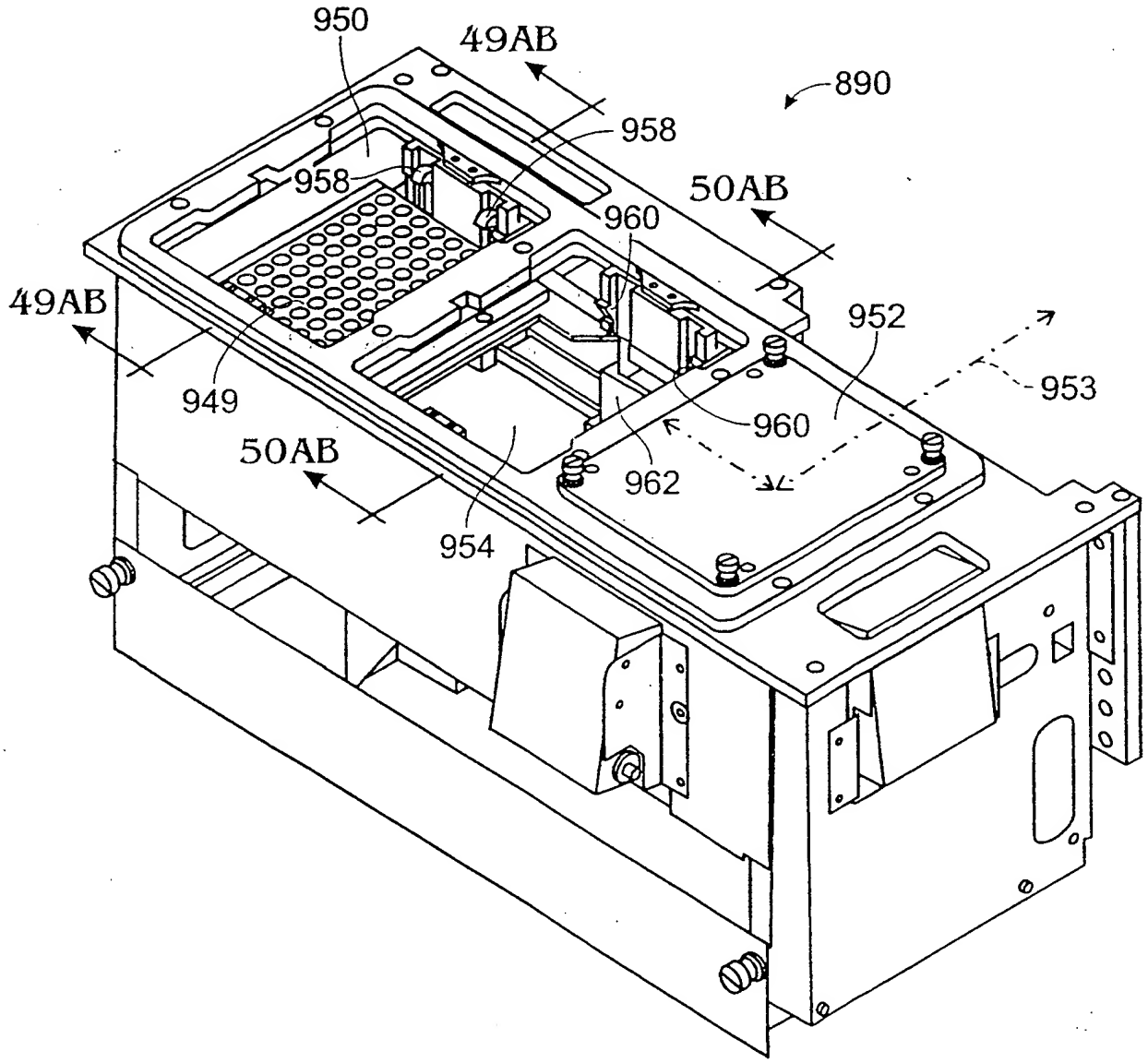


Fig. 49A

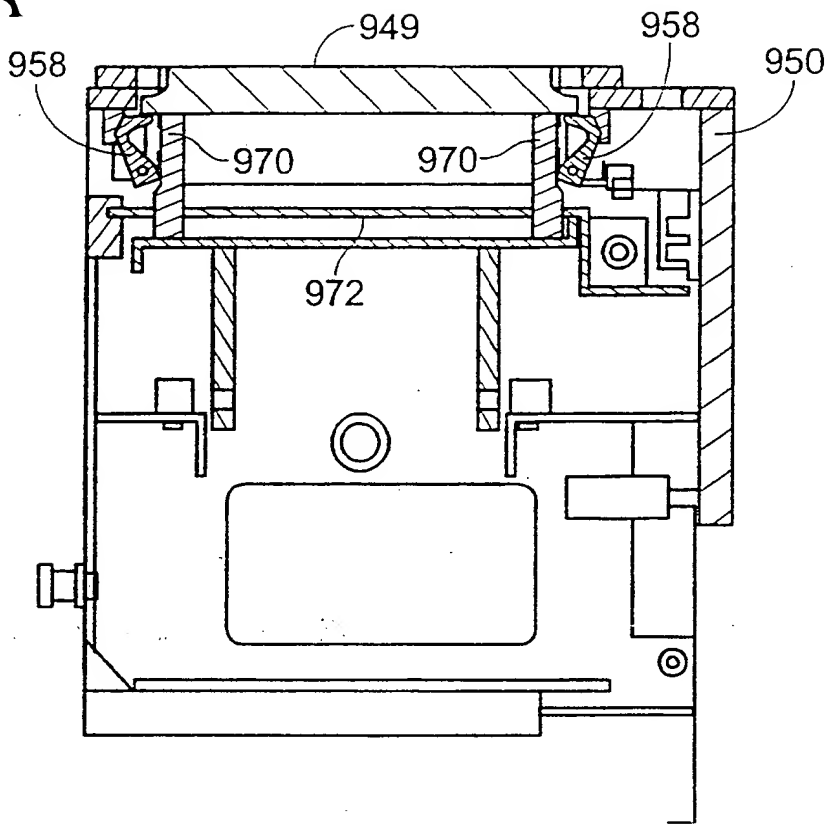


Fig. 49B

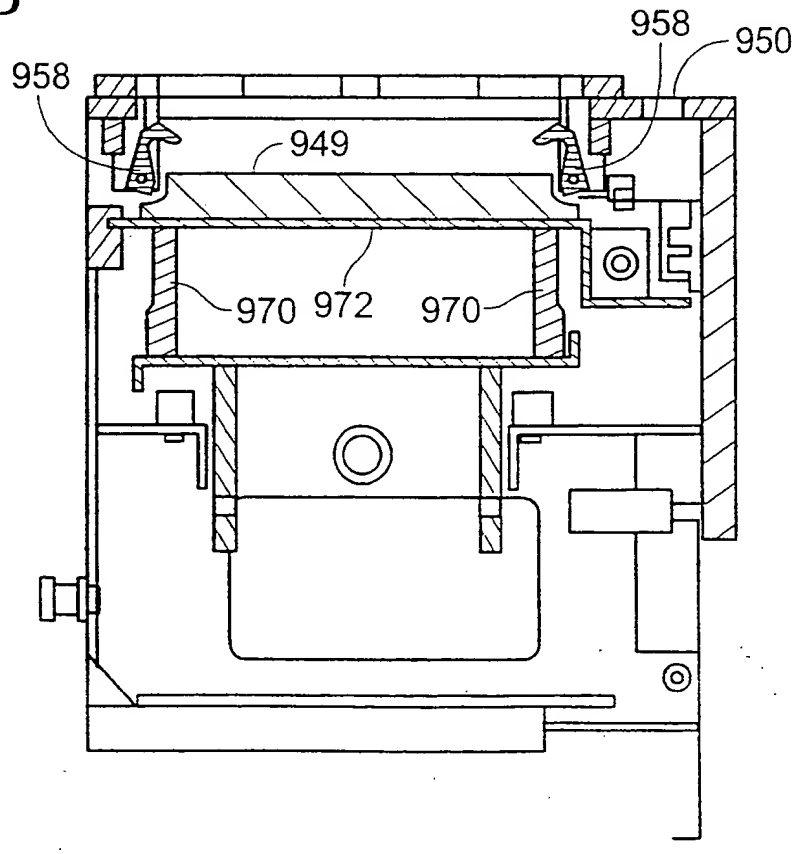


Fig. 50A

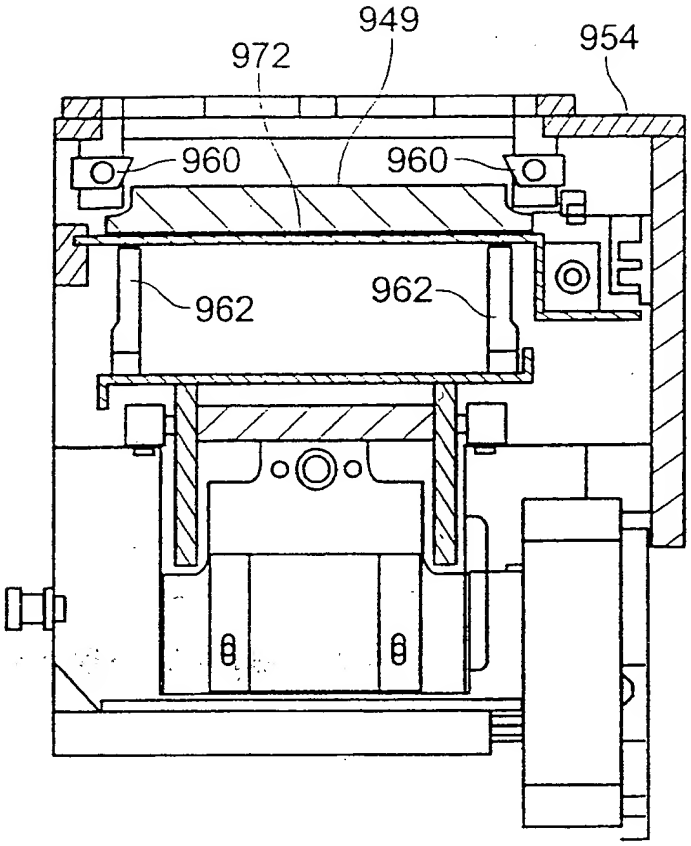
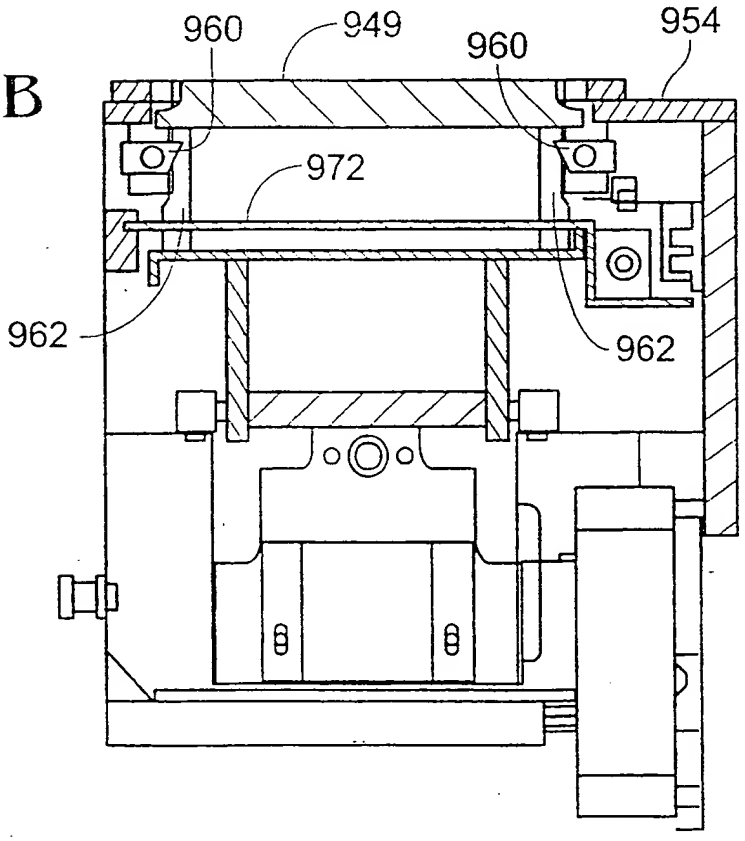


Fig. 50B



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14575

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01N 21/64, 21/66, 35/02.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/52, 63, 65, 67, 82.05, 82.08, 104; 436/43, 48, 164, 165, 172, 435/288.4, 288.7; 250/227.23, 458.1, 461.2; 356/318, 319, 320

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,491,343 A (BROOKER) 03 February 1996, figures 2 and columns 1-3.	1-5, 15-21, 30-38 and 41-46
X -- Y	US 5,206,568 A (BJORNSON et al.) 27 April 1993, figures 1-4 and its appropriate description.	63-69, 72, 74, 75, 79-82, 95, 101, 102, 108, 109, 111, 112, 114-118, 122, 123, 129 ------- 71, 73

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 29 JANUARY 1999	Date of mailing of the international search report 08 FEB 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Long V. Le Telephone No. (703) 308-0651

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14575

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,772,453 A (LISENBEE) 20 September 1988, figures 3, 11-13.	149-151, 159, 163-167, 169, 170
X -- Y	US 5,592,289 A (NORRIS) 07 January 1997, figures 1-6.	208-215 -------- 216, 217
Y	US 5,384,093 A (OOTANI et al.) 24 January 1995, figures 1-4	238-245
A	US 4,873,633 A (MEZEI, LOUIS M. et al.)10 October 1989, figures 2 and 13.	130-135

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14575

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-48, 63-107, 108-129, 130-135, 139-145, 149-151, 159-183, 188-193, 208-217, 218-245, and 265-270

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14575

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

422/52, 63, 65, 67, 82.05, 82.08, 104; 436/43, 48, 164, 165, 172, 435/288.4, 288.7; 250/227.23, 458.1, 461.2; 356/318, 319, 320

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-48, drawn to an apparatus for detection of light from a composition.
Group II, claims 49-53, drawn to a light switching module.
Group III, claims 54-58, drawn to a method of controlling light sources using a switching mechanism.
Group IV, claims 59-60, drawn to an apparatus with plural light sources and means for positioning the sample.
Group V, claims 61-62, drawn to an apparatus having a detector selection device that permits selection of different detectors for different applications.
Group VI, claims 63-107, drawn to an apparatus having an automatic registration means.
Group VII, claims 108-129, drawn to an apparatus with an optical relay structure for sensing sample volume.
Group VIII, claims 130-135, drawn to a photoluminescence detecting apparatus having a confocal optical element.
Group IX, claims 136-138, drawn to a method of automatically bringing a succession of compositions into register for analysis.
Group X, claims 139-145, drawn to a device for detecting light from a sample having means to properly position the optical detection head .
Group XI, claims 146-148, drawn to a chemiluminescence detecting device with a mask structure.
Group XII, claims 149-151, drawn to a chemiluminescence detecting device with a baffle.
Group XIII, claims 152-156, drawn to a chemiluminescence detecting device with means to control a specific spacing.
Group XIV, claims 157-158, drawn to a device having a plurality of optical relay structures.
Group XV, claims 159-183, drawn to a device for transmitting through an aperture.
Group XVI, claims 184-187, drawn to a method of light tight switching between two light fixtures.
Group XVII, claims 188-193, drawn to a device for holding an optical filter.
Group XVIII, claims 194-195, drawn to a tool for loading an optical filter into a holder.
Group XIX, claims 196-199, drawn to an optical filter holder system.
Group XX, claims 200-207, drawn to an optical filter wheel module.
Group XXI, claims 208-217, drawn to a support device for a sample container.
Group XXII, claims 218-245, drawn to an apparatus for the transport of microplates.
Group XXIII, claims 246-249, drawn to an automated analyzer having an analyzer unit and multiple loading stations.
Group XXIV, claims 250-264, drawn to a control unit for an automated analyzer.
Group XXV, claims 265-270, drawn to an apparatus for measuring the polarization of emitted luminescence.
Group XXVI, claims 271-272, drawn to a method for quantifying an optical signal.

The inventions listed as Groups I-XXVI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: each of the groups are drawn to different inventive concepts as evidenced by their above descriptions such that each does not share a special technical relationship with any of the other groups.